Diffusion Spectrum MRI Tractography Reveals the Presence of a Complex Network of Residual Myofibers in Infarcted Myocardium

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**Background**—Changes in myocardial microstructure are important components of the tissue response to infarction but are difficult to resolve with current imaging techniques. A novel technique, diffusion spectrum MRI tractography (DSI tractography), was thus used to image myofiber architecture in normal and infarcted myocardium. Unlike diffusion tensor imaging, DSI tractography resolves multiple myofiber populations per voxel, thus generating accurate 3D tractograms, which we present in the myocardium for the first time.

**Methods and Results**—DSI tractography was performed at 4.7 T in excised rat hearts 3 weeks after left coronary artery ligation (n=4) and in 4 age-matched controls. Fiber architecture in the control hearts varied smoothly from endocardium to epicardium, producing a symmetrical array of crossing helical structures in which orthogonal myofibers were separated by fibers with intermediate helix angles. Fiber architecture in the infarcted hearts was severely perturbed. The infarct boundary in all cases was highly irregular and punctuated repeatedly by residual myofibers extending from within the infarct to the border zones. In all infarcts, longitudinally oriented myofibers extending toward the basal-anterior wall and transversely oriented myofibers extending toward the septum lay in direct contact with each other, forming nodes of orthogonal myofiber intersection or contact.

**Conclusions**—DSI tractography resolves 3D myofiber architecture and reveals a complex network of orthogonal myofibers within infarcted myocardium. Meshlike networks of orthogonal myofibers in infarcted myocardium may resist mechanical remodeling but also probably increase the risk for lethal reentrant arrhythmias. DSI tractography thus provides a new and important readout of tissue injury after myocardial infarction. *(Circ Cardiovasc Imaging. 2009;2:206-212.)*

**Key Words:** myocardial infarction ■ fiber architecture ■ MRI ■ diffusion ■ myocardium

Methods to determine left ventricular ejection fraction and the presence of cardiac wall motion abnormalities have become accepted organ-scale indicators of cardiac mechanics and function. However, these measures are limited in their ability to discern the structural basis underlying the development of heart failure and lethal ventricular arrhythmias. There is thus intense interest in the development of noninvasive imaging techniques that provide novel readouts of myocardial structure and function and have the potential to characterize the microstructural response of the myocardium to injury and elucidate potential mechanistic links between molecular and organ scale pathology.1,2

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**Editorial see p 169**

**Clinical Perspective on p 212**

As demonstrated in pioneering histological studies,3 myofibers in normal myocardium form a series of crossing helical structures, in which the helix angle (angle at which the myofiber spirals around the long axis of the left ventricle) varies smoothly from a left-handed helix (0° to negative 90°) in the subepicardium to a right-handed helix (0° to 90°) in the subendocardium.3 Alterations in this myofiber pattern after myocardial infarction and in various cardiomyopathies have been detected both histologically and with noninvasive im-
aging techniques. However, current noninvasive imaging techniques are unable to visualize small groups of myofibers as continuous and highly resolved 3D anatomic entities. Changes in myocardial fiber architecture have thus often been inferred from changes, measured at discrete points in the myocardium, in the average helix angle and the fractional anisotropy of the myofibers in that voxel. Although this approach has utility, the ability to image myofibers as finely resolved 3D tracts would represent a significant advance and probably would provide novel insights into both mechanical and electric events in the injured myocardium.

Diffusion-weighted MRI exploits the preferential diffusion of water along the direction of muscle and nerve fibers. Diffusion tensor MRI (DTI) can be used to image the average direction of water diffusion in a voxel and derive a primary diffusion vector (primary eigenvector) for that voxel. The recent development of diffusion spectrum MRI tractography (DSI tractography), however, provides a platform to image myocardial fiber architecture with an unheralded level of detail and accuracy. Tractography involves the integration of individual diffusion vectors in a 3D field to yield continuous individual fibers and has been performed with DTI datasets in the brain and to a lesser extent in the tongue and heart. Diffusion spectrum MRI (DSI), however, supports the creation of significantly more robust tractograms because it is able to resolve multiple individual diffusion vectors per voxel rather than only the single composite vector produced by DTI. DSI tractography in the brain and tongue has resolved complex and converging fiber anatomy with significantly greater accuracy than DTI.

In the current study, DSI tractography resolves, for the first time, 3D myocardial fiber architecture with both high angular and spatial resolution. Moreover, this method provides a platform for the robust visualization of normal myofiber anatomy and the changes in 3D myofiber architecture occurring in infarcted hearts. Using DSI tractography, we demonstrate a pattern in normal myocardium of crossing helical myofiber tracts, with the helix angle varying smoothly from the endocardium to the epicardium. After induced myocardial infarction, we observed that the normal architectural pattern is replaced in parts of the infarct by a meshlike network of orthogonally oriented residual myofibers, extending from within the infarct to the septal and basal border zones. We propose that this configuration of myofiber anatomy has important implications for both mechanical remodeling and electric conduction in patients who have had a myocardial infarction and thus has broad clinical and translational relevance.

Methods

Principles of DSI Tractography

The physical basis of DSI tractography is described briefly below. The reader interested in a more mathematical description of the technique is referred to the supplementary materials. Diffusion is a physical property that represents the random translational motion of water molecules in tissue and is principally affected by the location of diffusional barriers such as membranes or cytoskeletal fibers. In muscular tissue, diffusion is greatest along the direction of individual or populations of muscle fibers due to their elongated and cylindrically symmetrical geometry. Conversely, diffusion is smallest when normal to the surface of a myofiber.

DSI acquisitions are assembled by sampling q-space, where q-space is a formalism representing diffusion weighting as a function of the strength and direction of the magnetic field gradient applied during the MRI experiment. Each voxel in physical 3D space has a unique diffusion signature representing the sum of all molecular diffusion events occurring within the indicated tissue. The more a directionally specific diffusion gradient is aligned with the particular fibers in the voxel, the greater the attenuation of the MR signal will be. In contrast to conventional DTI, which involves 6 diffusion-encoding gradients, DSI characteristically uses 515 diffusion-encoding gradient vectors. Each point in q-space represents the MR signal intensity in the voxel during the application of a particular q-vector. The MR signal is brightest when the q-vector is orthogonal to fiber direction and most attenuated (weakest) when it is applied along the direction of fiber orientation. An inverse Fourier transform of q-space yields a probability density function of fiber orientation per voxel and may include multiple local maxima, each denoting a distinct fiber population. By convention, the probability density function is converted into an orientation distribution function by radially integrating the probability density function, producing a probability distribution that is a function of only of fiber angle. The number of directions in which the 3D diffusion function (q-space) is sampled translates into the maximum possible angular resolution of the technique.

Tractography constructs fiber tracts by determining a set of streamlines from the vector directions in the orientation distribution function vector field, with intervoxel connectivity determined by a threshold vector angle. The tractography algorithm is constructed such that the tract assumes a path of minimum angular difference. Similarly, if the voxel contains 2 or more compatible paths, the tract will take that of the least angular difference. Fiber tracts in the myocardium are encoded by the helix or spiral angle they make with the long axis of the left ventricle.

Experimental Protocol

Excised hearts from 4 normal and 4 infarcted adult Sprague-Dawley rats were studied. Infarction was produced by permanent suture ligation of the left anterior descending coronary artery. After a 3-week interval, the hearts were perfusion-fixed and excised under deep surgical anesthesia with pentobarbital. Perfusion-fixation of the myocardium was achieved by cannulating the inferior vena cava and infusing a 4% paraformaldehyde solution, after which the excised hearts were stored in a 1% paraformaldehyde solution. The hearts from the age-matched control (noninfarcted) rats were perfusion-fixed and excised in an identical manner. All experiments were performed in accordance with regulations for the humane care of laboratory animals at our institution.

Diffusion-weighted MRI of the excised hearts was performed on a 4.7-T horizontal bore magnet (Biospec 4.7T, Bruker, Billerica, Mass) equipped with a 400-mT/m (120-mm internal diameter) gradient. The hearts were immersed in the fluorocarbon Fomblin (Auszinom, NJ) and imaged with a tailored solenoid radiofrequency coil. A 3-choplanar sequence was used with an isotropic spatial resolution of 0.4 mm and echo time of 39 ms. Diffusion encoding, after the 90° excitation pulse, was produced by 2 gradient pulses separated by a 180° refocusing pulse. The maximum b-value (diffusion weighting term proportional to the square of the diffusion gradient multiplied by the diffusion time) was chosen to attenuate the myocardial signal completely (approximately 1000). The repetition time between adjacent q-vectors was adjusted to produce a signal to noise ratio >100 in the presence of a b-value of zero and ranged from 1000 to 1500 ms. This resulted in an imaging time (515 q-vectors, no parallel acquisition, repetition time of 1000 to 1500 ms) of approximately 12 hours for each heart.

After imaging, the hearts were sectioned for the histological assessment of overall morphology and myofiber orientation, using hematoxylin-eosin and Masson trichrome staining. The hearts were cut longitudinally in the 4-chamber (horizontal long axis) orientation in 5-μm-thick sections beginning on the anterior free wall surface of the left ventricle. A semiquantitative correlation score between fiber
architecture in the infarct by DSI and by histology was derived by 2 observers. A fiber was assigned a score of 1 if its location and course on the DSI tractograms replicated its histological form extremely closely. If a good but incomplete correlation was seen between DSI and histology, the fiber was assigned a score of 0.5, and, if no correlation was seen, a score of zero. Postprocessing of the DSI datasets, including generation of the orientation distribution functions and DSI tractograms, was performed using software (Diffusion Toolkit, TrackVis) developed in our center. The tractograms were generated either as projection images of the entire heart or as tomographic reconstructions, where only fibers passing through a prescribed 2D slice (0.4 mm thick) or a spherical region of interest (radius ranging from 1 to 8 voxels) were displayed. Nodes of orthogonal myofiber intersection or contact (NOMIC) were detected by sweeping a 0.27 mm³ (radius equal to 1 voxel) spherical region of interest across areas of infarcted myocardium. A NOMIC was defined at each point where orthogonal myofibers passed through the same 0.27-mm³ region of interest, without the presence of intervening myofibers. A minimum spacing of 1 voxel was placed between successive NOMICs.

Results
As shown in Figure 1, DSI tractography robustly resolved the transmural variation in myofiber helix angle. In normal hearts, myofibers in the midmyocardium were aligned circumferentially around the long axis of the left ventricle (zero helix angle), subendocardial fibers had a positive or right-handed helix angle, and myofibers in the subepicardium had a negative or left-handed helix angle. The transition in fiber helix angle from endocardium to epicardium occurred in a smooth and symmetrical manner, with little dispersion in the helix angle at a given transmural plane.

Fiber architecture in normal rat myocardium is shown in more detail in Figure 2. Fiber tracts in both the subendocardium (Figure 2A and 2B) and subepicardium (Figure 2D and 2E) of the lateral wall form convex half-turns of a spiral. However, the fibers in the subendocardium of the lateral wall are aligned from the posterior-base to antero-apex (Figure 2F and 2G), forming a positive right-handed helix, and those in the subepicardium (Figure 2I and 2J) from the antero-base to the postero-apex forming a negative or left-handed helix. The circumferential fiber tracts in the midmyocardium formed a single complete turn around the minor axis of the left ventricle on the DSI tractograms (Figure 2C and 2H). The helix angle at identical transmural locations in the septum was equal to that in the lateral wall. However, right-handed fibers in the septum coursed from the antero-base to the postero-apex and left-handed fibers from the postero-base to the antero-apex, completing a loop of their respective helices.

Changes in myofiber architecture in the infarcted hearts were best visualized in an orientation looking down onto the anterior and lateral walls of the left ventricle (Figure 3). In the control hearts, a regular network of myofiber sheets consisting predominantly of subepicardial (yellow-green) and midmyocardial (blue) fibers was visualized in this orientation (Figure 3). A profound loss of myofibers was seen in the infarcted myocardium, and myofiber tract length in the entire heart was reduced from 10.5±0.7 mm in the normal hearts (mean±SEM) to 6.9±0.8 mm in the infarcted hearts (P<0.05). The infarct boundary in all cases was highly porcine myocardium.
irregular and punctuated at frequent intervals by strands of residual myofibers extending from within the infarct to the basal and septal border zones (Figure 3). Far fewer and significantly smaller strands of residual myofibers extended from the infarct into the border zones at the anterolateral apex (Figure 3). A high degree of correlation (correlation score, \(0.79\)) was seen between the myofiber patterns on the DSI tractograms and the corresponding histological sections through the left ventricles of the infarcted hearts (Figure 3).

In normal myocardium, subendocardial fibers and orthogonally oriented mid/subepicardial fibers coursed through completely different transmural planes (separated by myofibers with intermediate helix angles) and thus did not intersect (Figure 4). In all 4 infarcted hearts, however, longitudinally oriented myofibers (pink) extended from within the infarct to the border zones in the basal anterior and lateral walls and formed a complex network of orthogonal myofibers with transversely oriented mid/subepicardial fibers (blue-green) that course from the infarct to the septum. C, Hematoxylin-eosin–stained section of normal myocardium (demarcated by the black lines in panel A). D, Masson trichrome–stained section of the infarcted heart, showing intact strands of transverse myofibers (brown) coursing from the infarct to the septum. E, hematoxylin-eosin–stained section showing longitudinal strands of myofibers extending from the infarct to its basal border zone. A high degree of correlation is seen between the DSI tractograms and their corresponding histological sections.

**Discussion**

Despite significant advances in delineating the molecular basis of myocardial injury, the translation of this knowledge into novel therapies has been slow. A compelling need thus exists to develop novel noninvasive imaging techniques capable of resolving myocardial pathology at the microstructural and molecular levels to accelerate the translation of this knowledge into the clinical setting. In this study, we present the first application of DSI tractography in the myocardium and show that the technique is able to resolve myocardial fiber architecture in the intact heart with an exceptional level of detail and accuracy. We show, moreover, using DSI, that a complex network of residual myofibers is present in the infarct zone with myofiber architecture supporting the formation of NOMICs averaged (mean ± SEM) 33.8 ± 3.4% and was found in the more basal and septal portions of the infarcts, as shown in the infarcted heart in Figure 5. Within this area, an average of 7 ± 0.7 (mean ± SEM) NOMICs were present in each of the infarcted hearts.
infarcted myocardium and that these fibers form NOMICs within the infarct.

MRI is uniquely able to image muscle and nerve tracts due to its sensitivity to the diffusion of water. During DTI, 6 diffusion-encoding gradients are applied to determine the direction of preferred diffusion (primary eigenvector), which corresponds to the long axis of myofibers. The mean helix angle in a voxel, derived from a composite primary eigenvector, can be used to approximate the average myofiber orientation in that voxel. DTI has been used to demonstrate a loss of right-handed (subendocardial) fibers and a decrease in fiber anisotropy in infarcted myocardium.

Multivoxel tracts have been constructed in the brain and to a lesser extent in the tongue and myocardium using DTI. However, DTI is significantly limited in its angular and spatial resolution and cannot fully resolve converging, crossing, or complex fiber geometries. DSI, however, is able to resolve multiple distinct fiber populations per voxel and...
has demonstrated the capacity to visualize complex and intersecting fiber tracts in the tongue and the brain. The ability of DSI tractography to detect multiple fiber tracts in a single voxel allowed the presence of residual orthogonal myofibers and NOMICs in the infarcted myocardium to be detected in volumes as small as 0.27 mm\(^3\) in this study (Figures 4 and 5).

The presence of a network of orthogonally oriented residual myofibers within the infarct is likely to provide tensile strength and resist infarct expansion and remodeling. Fewer residual myofibers were seen in the apical portions of the infarcts (Figure 5), which may explain the propensity for aneurysm formation in this location. The presence of a network of residual myofibers within an infarct, however, could also constitute a substrate that is highly susceptible to electric reentry and ventricular tachycardia. The formation of a meshlike myofiber network within the infarct is thus likely to provide mechanical advantage at the cost of significant electrophysiological risk.

DSI tractography is a 3D imaging technique in which fiber tracts can be visualized from any orientation and can follow curved trajectories in 3D space. Histological sections, however, are inherently 2D. Moreover, the DSI tractograms in this study were visualized either as projection images or as 0.4-mm-thick tomographic reconstructions, whereas the histological sections were only 5 μm thick. A histological section tangential to the myocardium is thus less likely than a DSI tractogram to visualize both subendocardial and subepicardial fibers. Despite these differences, the residual myofibers seen with DSI tractography in the infarcted hearts were well observed in the corresponding histological sections, with a high degree of correlation between the 2 techniques (Figures 3 and 5).

The effect of tissue fixation on diffusion MRI has been extensively studied. Tissue fixation reduces the overall diffusion scalar but does not change the relative magnitudes or directions of the diffusion vectors. Although stronger b-values (diffusion gradients) are required after fixation, DTI of fixed tissue has been shown to produce fiber orientations and tractograms identical to those obtained in live and fresh unfixed tissue. It has also been suggested that in the myocardium DTI of fixed tissue may produce more accurate data than that obtained in fresh perfused tissue due to the absence of flow artifacts and the ability to obtain data with higher signal to noise.

The ability of DSI tractography to resolve complex changes in myofiber architecture in infarcted myocardium has been demonstrated in this study. Further study will be needed to determine whether these changes are replicated in large animals and humans and to fully characterize their electrophysiological impact. Diffusion MRI of the human myocardium has been performed in vivo, and a clear pathway to clinical translation of DSI tractography in the myocardium exists: Scan times in humans will be reduced by the shorter T1 (longitudinal relaxation time) of the myocardium at clinical field strengths and the consequent ability to shorten the repetition time, adjustment of the DSI algorithm will be performed to achieve adequate spatial and angular resolution with significantly fewer than 515 diffusion-encoding gradients, and highly accelerated parallel acquisitions with 32 and 128 channel cardiac arrays will be used.

In conclusion, we have applied DSI tractography ex vivo to image myocardial fiber architecture with an unheralded level of precision. Moreover, the potential of a meshlike network of orthogonal myofibers to persist in portions of infarcted myocardium has been identified. Our study demonstrates that DSI tractography has the capacity to robustly identify microstructural changes in myofiber anatomy and provide readouts relevant to both mechanical remodeling and electric conduction in the diseased ventricle. Although further study will be required, DSI tractography has the potential to become a highly valuable imaging technology in cardiovascular medicine.

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Disclosures
None.

References
Thus has the potential to become a highly valuable tool in the cardiovascular imaging armamentarium. The translation of the technique to humans will require some modifications but is feasible. DSI tractography could thus provide valuable insights into both electrical and mechanical events in infarcted myocardium. We show, moreover, that these residual myofibers can form abnormal connections with each other. The translation of the technique to humans will require some modifications but is feasible. DSI tractography could thus provide valuable insights into both electrical and mechanical events in infarcted myocardium. We show, moreover, that these residual myofibers can form abnormal connections with each other.

Muscle fibers in the myocardium spiral around the left ventricle with a helix angle that is determined by their transmural location. This myofiber architecture influences both the mechanical and electrical properties of the left ventricle and is perturbed in injured myocardium. The impact of altered myofiber architecture, however, remains poorly understood in large part because of the difficulty in assessing this in vivo. In the current article, we describe a technique known as diffusion spectrum MRI tractography (DSI tractography) to image 3D myofiber architecture in vivo. The technique is based on the preferential diffusion of water along myofibers, which creates a detectable change in the MR signal when an appropriate magnetic gradient is applied. DSI tractography represents a significant advance over previously developed techniques in that multiple fiber populations can be resolved in a single voxel, supporting the construction of robust myofiber tractograms. DSI tractography was used to image normal and infarcted rat myocardium in this study. We show that a complex network of residual myofibers persists within portions of the infarcted myocardium, linking the infarct zone to the border zone. We show, moreover, that these residual myofibers can form abnormal connections with each other. The use of DSI tractography could thus provide valuable insights into both electrical and mechanical events in infarcted myocardium. The translation of the technique to humans will require some modifications but is feasible. DSI tractography thus has the potential to become a highly valuable tool in the cardiovascular imaging armamentarium.
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Supplementary Methods

Mathematical Basis of generating images with diffusion spectrum MRI (DSI) with tractography.

Diffusion spectrum imaging (DSI) resolves morphologically complex myoarchitecture by obtaining the average molecular diffusion function within a region of tissue and depicting it as the probability that a given water molecule will undergo direction-specific motion within a given period of time. Diffusion is a physical property, which represents the random translational motion of water molecules in tissue, and is principally affected by the location of diffusional barriers such as membranes or cytoskeletal fibers. In muscular tissue, diffusion is greatest along the direction of individual or populations of fibers due to their elongated and cylindrically symmetric geometry. Consequently, diffusion measurements can be used to derive information regarding three-dimensional fiber orientation in situ. Stejskal and Tanner, solved for the amount of diffusion attenuation due to an applied diffusion weighting gradient \( \tilde{g} \) of duration \( \tilde{\delta} \):

\[
M(\tilde{q}, \tau) = M(0, \tau) \int P(\tilde{R} | \tau) \exp(i\tilde{q} \cdot \tilde{R}) d\tilde{R}
\]  

(1)

where \( \tilde{q} \) is equal to q-value, \( M \) is the signal intensity, \( \tau \) is the diffusion time, \( \tilde{R} \) is the diffusion distance, and \( P \) is the average probability distribution function of diffusion (PDF). We additionally note the term, b-value, which relates to the maximum overall diffusion weighting for a set of diffusion weighted image acquisitions, and is determined by:

\[
b = \left\| \tilde{q}_{max} \right\|^2 \tau
\]

The PDF \( P(\tilde{R}, \tau) \) is the inverse Fourier transform of (1):

\[
P(\tilde{R}, \tau) = F^{-1}[M(\tilde{q}, \tau)],
\]

(2)
where \( F^{-1} \) denotes the inverse Fourier transform. The spacing between \( \vec{q} \) vectors defines the field of view and the maximum \( \vec{q} \) vector defines the resolution of the PDF. The values of \( M(\vec{q}, \tau) \) are placed in a matrix with indices given by the indices of the \( \vec{q} \) vectors, and the 3D inverse discrete Fourier transform is computed. Complete DSI acquisitions are assembled by sampling q-space, where q-space is a formalism representing diffusion weighting as a function of the strength and direction of the magnetic field gradient applied during the MRI experiment. By convention, the PDF is converted into an orientation distribution function (ODF) by radially integrating the PDF by the magnitude of \( \vec{R} \):

\[
ODF(\hat{u}, \tau) = \int P(\rho \hat{u}, \tau) \rho d\rho,
\]

where \( \hat{u} \) is a unit vector in the direction of \( \vec{R} \). This produces a probability distribution that is a function only of fiber angle. By this conversion there are a finite number of directions in which the 3D diffusion function is sampled, which translates into the maximum possible angular resolution.

Tractography constructs a set of unique connections involving vector directions in a vector field by determining a set of streamlines based on the solution of the following differential equation

\[
\frac{d\vec{S}(s)}{ds} = \vec{v}(\vec{S}(s)),
\]

where \( \vec{S}(s) \) is the streamline, \( s \) is a path coordinate along \( \vec{S} \), and \( \vec{v} \) is the vector field. Equation (4) demonstrates that the streamline will be tangent to the vector field at all points. Here, intervoxel angle similarity is a driving factor in determining the trajectory that a tract may take, where a certain angular threshold must be met to establish intervoxel connectivity. In the present work we employed an angular threshold of \( < \pm 17.5^\circ \) to define tract continuity. (Increasing the
threshold to < +/- 35° did not significantly alter the resulting tractograms and did not produce an increase in the number of resolved fibers within the infarct zone.) The tractography algorithm is constructed such that the tract takes the path of minimum angular difference. Similarly, if the voxel contains two or more compatible paths, the tract will take that of the least angular difference. Fiber tracts in the myocardium are then encoded in terms of the helix or spiral angle they make with the long axis of the left ventricle.

The reader interested in further background reading on the principles and development of Diffusion Spectrum MRI and tractography is referred to the reference list below.²⁻⁷

References (Supplement)


