Sequential Changes of Myocardial Microstructure in Patients Postmyocardial Infarction by Diffusion-Tensor Cardiac MR

Correlation With Left Ventricular Structure and Function

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Background—We used diffusion-tensor cardiac MR to investigate myocardial microstructure changes, including tissue integrity (mean diffusivity [MD], fractional anisotropy) and fiber architecture (helix angles) in patients with recent myocardial infarction (MI). This study aimed to investigate the sequential changes of myocardial microstructure and its relationships with changes of macrostructure and function of the left ventricle post-MI.

Methods and Results—Seventeen patients (age, 55.1±11.5 years; all men) participated in the follow-up study. Diffusion-tensor cardiac MR, cine gradient echo for left ventricle function, and late gadolinium enhancement for viability were measured from recent to chronic MI (median interval, 191 days). When compared with the remote zone, the infarct-adjacent zone showed overall increase of MD (2-way MANOVA, F1,16 =36.3; \( P<0.001 \)), decrease of fractional anisotropy (F1,16 =5.8; \( P=0.029 \)), and decrease of mean helix angles (F1,16 =62.0; \( P<0.001 \)). From recent to chronic MI, there was overall sequential decrease of MD (F1,16 =22.6; \( P<0.001 \)) and increase of fractional anisotropy (F1,16 =7.8; \( P=0.013 \)). Multiple linear regression showed that the improvement of wall thickening in the infarct-adjacent zone correlated with sequential decrease of MD in the infarct-adjacent zone (\( r=-0.70; P=0.002 \)) and increase of mean helix angles (ie, more right-handed helical myofiber reorientation, predominantly subendocardial location) in the remote zone (\( r=0.60; P=0.011 \)). Likewise, wall thickening in the remote zone correlated with MD in the remote zone (\( r=-0.72; P=0.001 \)) and mean helix angles in the infarct-adjacent zone (\( r=0.72; P=0.001 \)).

Conclusion—Diffusion-tensor cardiac MR suggests that sequential zonal improvement of tissue integrity and fiber architecture remodeling both associate with sequential recovery of zonal wall thickening of the left ventricle from recent to chronic MI. (Circ Cardiovasc Imaging. 2009;2:32-40.)

Key Words: imaging ■ magnetic resonance imaging ■ myocardial infarction ■ remodeling

Postinfarction late remodeling involves the left ventricle (LV) globally and is associated with time-dependent dilatation, distortion of ventricular shape, rearrangement of fiber architecture, and mural hypertrophy.1 Clearly, there is a great need for, and utility in, the in vivo acquisition of a wealth of cardiac microstructures such as geometry, fiber and sheet orientation, and cell populations to improve our ability to design strategies for effective restoration of myocardium postinfarction.2,3

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Recently, diffusion-tensor cardiac MR (DT-CMR) has emerged as a unique method for the nondestructive reconstruction of the fiber structure of the LV, which has been validated to have strong correspondence with fiber orientation by histological correlation4-6 and also has been modified to advance its...
application to the living human heart. \textsuperscript{7-10} In a previous report, we used DT-CMR to observe the alteration of tissue integrity, indicated by mean diffusivity (MD, also known as trace-apparent diffusion coefficient), fractional anisotropy (FA), and fiber architecture, indicated by helix angles (HA), in patients post-myocardial infarction (MI) at a median interval of 26 days. \textsuperscript{11} We found alteration of tissue integrity and fiber architecture, which had a significant correlation with the viability zones and regional wall function. When compared with the remote zone, the infarct-adjacent zone showed significant decrease of wall thickness and wall thickening at the macrostructure level of the LV, as well as significant decrease of tissue integrity, reflected by increased MD and reduced FA, increase of wall thickness and wall thickening at the macrostructure level, which had a significant correlation with the viability zones and regional wall function. To investigate the sequential change of tissue integrity and fiber architecture during myocardial healing and remodeling, we repeated the identical DT-CMR in patients from the previous study who were able and willing to participate in the continuing study. By observing sequential changes of macrostructure and microstructure and the relationships between them, we hypothesized that there is biomechanical relevance of the alteration of tissue integrity and fiber architecture participated in the remodeling process of the myocardium postinfarction, which could be revealed by DT-CMR.

**Methods**

**Subjects**

**Patients**

From the 37 patients enrolled in our previous study, \textsuperscript{11} we performed a follow-up study on those who satisfied the following inclusion criteria: (1) receiving the initial MR scan after onset of acute MI in the previous study, \textsuperscript{11} and (2) being clinically stable and cooperative for the MR scan. Twenty patients participated, but 3 patients were excluded due to suboptimal image quality, which were mainly caused by irregular heart rhythm during scanning. As a result, images of 17 patients (age, 55.1±11.5 years; New York Heart Association class I, n=13; class II, n=4; all men) were available for the study. The first MR was performed in the same protocol for interscan reliability.

**Healthy Controls**

To investigate the normal range and reproducibility of DT-CMR measurement of myocardial microstructure, we enrolled 7 age-matched healthy men without known history of cardiac disease as a control group (range, 45 to 65 years old). Except late gadolinium-enhanced imaging, we used the same MR pulse sequences as those applied to the patients. All control subjects received 2 MR examinations, 6 months apart, with the same protocol for interscan reliability.

**MR Acquisitions**

The study was performed on a 1.5 T imager (CVi, GE Healthcare, Milwaukee, Wis) with a dedicated quadrature cardiac surface coil (Nova Medical, Wilmington, Mass). The imaging protocol for the initial and follow-up studies was identical and was described in detail in our previous study. \textsuperscript{11}

**Fast Gradient Echo Cine for Macrostructure**

Localizers were first obtained to determine imaging planes in both 4-chamber and short-axis views. We retrieved and compared patients’ initial MR to ensure that slice locations were as identical as possible. Fast gradient echo ciné in short-axis view (repetition time/echo time/frame rate, 9.1 ms/9 ms/30°; slice thickness, 8 mm; views per segment, 80; field of view, 240 mm; matrix, 256×128; field of view, 240×320 mm; 1 average) was obtained for the assessment of regional LV wall function.

**DT-CMR for Microstructure**

The pulse sequence design of DT-CMR used in this study was described in detail previously. \textsuperscript{7} In brief, we used a double-gating stimulated-echo single shot echo planar imaging sequence in which 2 diffusion gradient pulses (oriented in 6 nonopposed edge centers of a cube; gradient strength, 40 mT/m; duration, 2 ms; diffusion sensitivity, 300 s/mm\textsuperscript{2}) were applied at an identical cardiac phase in 2 consecutive heart beats, to avoid signal dropout due to cardiac motion. Previously, we showed that myocardial strain could influence diffusion measurement and proposed to apply diffusion gradient pulses at the midsystolic phase, so called “sweet spot,” to minimize the strain effect. \textsuperscript{8} We reviewed the cine gradient echo in 4-chamber and short-axis view to determine the trigger delays of end-systole and end-diastole. The mid-systole was determined as the midpoint between end-diastole and end-systole. The sweet spots of infarct-adjacent zone and remote zone were determined separately. If the sweet spots were different, 2 were averaged and used for trigger delay.

DT-CMR was performed with intermittent breath holds. Each breath hold spanned 14 heartbeats to obtain 6 diffusion-weighted images and a reference image with null gradient. We acquired 3 DT-CMR slices in short-axis view at mid-LV level (slice thickness, 8 mm; interslice gap, 4 mm), therefore composing a “midventricular volume” covering 32-mm thickness at voxel resolution of 1.88×1.88×8 mm. The imaging parameters for echo-planar image were field of view of 240 mm, matrix size of 128×128, repetition time/echo time of 2 R-R interval/42 ms, average of 12, and duration of the signal-readout of 640 μsec. To minimize misregistration of DT images acquired at different breath holds, we coached the patients to hold the breath at “quiet end expiration,” and applied a plethysmography to monitor the respiratory movement to ensure images acquired at a consistent breath-holding position.

**Late Gadolinium-Enhancement MR for Viability Zone**

Late gadolinium-enhancement (LGE) MR was used to identify the infarct area. \textsuperscript{12} After a delay interval of 8 to 15 minutes after a bolus of 0.2 mmol/kg of gadopentetate dimeglumine, a series of 180° inversion-recovery segmented gradient-echo T1-weighted images was acquired in the same imaging planes as for DT-CMR and cine fast gradient echo. Figure 1 illustrates an example of LGE-CMR in a patient with anterior MI showing LGE zones within anterior and lateral myocardium. Late gadolinium-enhancement MR was performed at the mid-LV level, “midventricular volume,” the data analysis of LGE-MR viability map and regional LV function were performed on this volume only. \textsuperscript{11} We then averaged the measurements from the 3 slices to represent the volume data, which was categorized into 2 viability zones; therefore, a volume data with 2 zones represented the data set of a single subject. Combining the initial and follow-up MR as 1 pair, a total of 17 pairs of data sets entered the data analysis for the 17 patients. For healthy control, similar procedure for midventricular volume was performed; however, there was no difference in terms of viability zones and all measurements were averaged over the whole volume.

**Evaluation of Myocardial Macrostructure**

**Viability Zones and Wall Thickness**

High-resolution LGE-MR was used for zonal segmentation of the viability. Using commercial software (MASS, GE Healthcare) on an
Regional LV Wall Thickening

Evaluation of LV wall function was performed on the fast gradient echo cine images with the modified centerline method by a semiautomated program (MASS) as described in the literature. One author (C.K.R.) traced the epicardial and endocardial contours without knowledge of the infarct-related arteries and viability maps by LGE-MR. Regional wall thickness and wall thickening were evaluated. The wall thickening was expressed by (wall thickness of end-systole − wall thickness of end-diastole)/wall thickness of end-diastole × 100%.13

Evaluation of Myocardial Microstructure

Tissue Integrity and Fiber Architecture

The details of the calculation of MD, FA, and HA were described previously.13 Each DTI data set was analyzed by one author (S.M.Y.) blinded to the results of LV wall function and LGE-MR viability maps. The program was institute-developed using Mathematica (version 4.0, Wolfram Research Inc). We did quality assurance of the images by discarding the images that are morphologically different from a reference image. We coregistered the images of the same diffusion-sensitivity gradient to the reference image by performing in-plane translation to achieve maximum correlation of image intensity. The 2 MR data of a patient were analyzed in pair with the same setting of parameters, but in a random order blinded to observer (S.M.Y.).

To evaluate the myocardial tissue integrity, we measured MD and FA of the diffusion tensor. MD was quantified as the mean of the 3 eigenvalues of the diffusion tensor. FA represents the degree of deviation of a diffusion ellipsoid from a sphere and was quantified as the SD of the eigenvalues of the diffusion tensor normalized by the “magnitude” of the 3 eigenvalues of the diffusion tensor. Myocardial fiber orientation at each pixel was defined by the first eigenvector of the diffusion tensor in the DT-CMR. Fiber HA was determined according to Streeter’s original convention,13 simplified to cylindrical coordinates for image analysis. To compare the difference in fiber orientations (ie, HA) across the 2 viability zones, we calculated the transmural average of HA as mean HA of each viability zone; in addition, we divided the fiber orientation into 3 groups with continuous-scale pseudocolored encoding on 128×128 matrix: (1) −90° to −30°, as LHF, mainly distributed in the subepicardium and pseudocolored as green hue; (2) −30° to 30°, circumferential fibers (CF), pseudocolored as blue hue; and (3) 30° to 90°, RHF, mainly distributed in the subendocardium, pseudocolored as red hue. Finally, the percentages of LHF, CF, and RHF in each viability zone were expressed as LHF%, CF%, and RHF%, respectively.

Sequential Changes of the Measurements

The sequential change of wall thickness and wall thickening were defined as (measurement at chronic MI − measurement at recent MI)/measurement at recent MI×100%. The sequential changes of DTI measurement were defined as (measurement at chronic MI − measurement at recent MI). The reproducibility of repeated DTI measurements in healthy control was evaluated by variability, defined as absolute difference divided by average of 2 measurements×100%; and coefficient of variance, defined as SD of absolute difference between 2 measurements divided by the average of the 2 measurements.

Statistical Analysis

Values of measurements of macrostructure (wall thickness and thickening) and microstructure (MD, FA, mean HA, LHF%, CF%, and RHF%) of each zone are expressed as mean±SEM. Otherwise, values such as age, days, ms are expressed as mean±SD. The viability zonal effect (2 zones, infarct-adjacent versus remote zone) and sequential effect (2 time points, recent versus chronic) within subject on the macrostructure and microstructure measurements were evaluated by 2-way (ie, zone and time point) MANOVA and paired t test. Relationships between sequential changes of microstructure versus that of macrostructure were evaluated by Pearson’s correlation coefficients. Multiple linear regression analysis was used to search MD, FA, and...
mean HA as potential associations of changes of wall thickness and thickening. \( P<0.05 \), 2-sided, was considered as significant. Statistical analysis was performed with SPSS 11.0 (SPSS Inc, Chicago, Ill). The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**General Patients Characteristics**

The infarct-related arteries involved left-anterior-descending artery in 9, circumflex artery in 2, and right coronary artery in 6 cases, and involved infarcted walls anterior in 10, septal in 3, inferior in 7, and lateral in 4 cases. Of the midventricular volume of interest where the microstructure also measured, the size of infarct-adjacent area was 31.5\( \pm \)10.5\% in recent MI and 28.2\( \pm \)9.5\% in chronic MI. The ejection fraction was 44\( \pm \)7\% in recent MI and 43\( \pm \)9\% in chronic MI.

**Changes of Myocardial Macrostructure**

Table 1 lists all the measurements of macrostructure and microstructure of the 2 viability zones, and the sequential pairwise comparison between recent and chronic MI. The differences between the remote zone and infarct-adjacent zone were also listed and compared for sequential changes.

There was overall decrease of wall thickness in the infarct-adjacent zone relative to the remote zone (2-way MANOVA, \( F_{1,16}=29.9; P<0.001 \)). Interval changes from recent MI to chronic MI showed sequential decrease of wall thickness in the infarct-adjacent zone (9.6\( \pm \)0.5 to 8.8\( \pm \)0.5 mm; \( P=0.003 \)), whereas sequential increase in the remote zone (10.4\( \pm \)0.6 to 11.2\( \pm \)0.5 mm; \( P=0.005 \)). The difference of wall thickness between the remote zone and infarct-adjacent zone was 0.7\( \pm \)0.3 mm in recent MI, and the difference progressed significantly to 2.4\( \pm \)0.3 mm in chronic MI (\( P<0.001 \)).

There was overall decrease of wall thickening in the infarct-adjacent zone relative to the remote zone (\( F_{1,16}=21.3; P<0.001 \)). There was no significant sequential changes of wall thickening in the infarct-adjacent zone (39.0\( \pm \)3.5 to 32.4\( \pm \)4.6\%; \( P=0.17 \)) and in the remote zone (55.9\( \pm \)5.9 to 62.9\( \pm \)5.5\%; \( P=0.15 \)), whereas the difference of wall thickening between the remote zone and infarct-adjacent zone showed progression from 16.9\( \pm \)4.2 in recent MI to 30.5\( \pm \)6.2 in chronic MI (\( P=0.020 \)).

The above findings indicated that the LV postinfarction underwent progressive eccentric remodeling of wall thickness and wall thickening from recent MI to chronic MI.

**Changes of Myocardial Microstructure**

There was overall increase of MD in the infarct-adjacent zone relative to the remote zone (\( F_{1,16}=21.3; P<0.001 \)). Interval changes from recent MI to chronic MI showed sequential decrease of wall thickness in the infarct-adjacent zone (9.6\( \pm \)0.5 to 8.8\( \pm \)0.5 mm; \( P=0.003 \)), whereas sequential increase in the remote zone (10.4\( \pm \)0.6 to 11.2\( \pm \)0.5 mm; \( P=0.005 \)). The difference of wall thickness between the remote zone and infarct-adjacent zone was 0.7\( \pm \)0.3 mm in recent MI, and the difference progressed significantly to 2.4\( \pm \)0.3 mm in chronic MI (\( P<0.001 \)).
infarct-adjacent zone ($9.2 \pm 0.5$ to $7.4 \pm 0.3 \times 10^{-6}$ cm$^2$/s; $P<0.001$) and in the remote zone ($8.1 \pm 0.5$ to $6.7 \pm 0.3 \times 10^{-6}$ cm$^2$/s; $P=0.001$) (Figure 2A). The difference of MD between infarct-adjacent zone and remote zone showed a trend of reduction from recent MI to chronic MI ($-1.1 \pm 0.2$ to $-0.7 \pm 0.1 \times 10^{-6}$ cm$^2$/s; $P=0.06$; Table 1; Figures 2A through 2C).

There was overall decrease of FA in the infarct-adjacent zone relative to the remote zone ($F_{1,16}=5.8; P=0.029$). There was a trend of increase of FA from recent MI to chronic MI in the infarct-adjacent zone ($0.25 \pm 0.01$ to $0.27 \pm 0.01; P=0.07$) and in the remote zone ($0.27 \pm 0.01$ to $0.29 \pm 0.01; P=0.018$; Figure 2B). The difference of FA between infarct-adjacent zone and remote zone had no significant interval change ($0.02 \pm 0.01$ to $0.02 \pm 0.01; P=0.59$).

Helical reorientation of fiber architecture was negative mean HA (more left-handed helical) in the infarct-adjacent zone and positive mean HA (more right-handed helical) in the remote zone ($F_{1,16}=62.0; P<0.001$). There was no significant interval change of mean HA between recent MI and chronic MI in the infarct-adjacent zone ($10.4 \pm 3.6^\circ$ to $10.8 \pm 2.1^\circ; P=0.91$) and in the remote zone ($13.1 \pm 1.5^\circ$ to $15.4 \pm 2.1^\circ; P=0.31$; Figure 2C). The difference of mean HA between infarct-adjacent zone and remote zone showed no significant interval change from recent MI to chronic MI ($23.5 \pm 3.9^\circ$ to $26.1 \pm 2.9^\circ; P=0.31$).

**Correlation of Sequential Changes of Myocardial Macrostructure Versus Microstructure**

In associating with the sequential changes of wall thickness, there was only one sequential change of microstructure showing significant correlation, ie, the sequential change of RHF% ($r=0.66; P=0.005$; Table 2; Figure 3).

There were several significant correlations between the sequential changes of wall thickening and microstructure. The sequential change of wall thickening in the infarct-adjacent zone correlated inversely with the sequential change of MD in the infarct-adjacent zone ($r=-0.70; P=0.002$) and the remote zone ($r=-0.53; P=0.029$), and correlated with the sequential change of mean HA in the remote zone ($r=0.60; P=0.011$) and the sequential change of RHF% in remote zone ($r=0.61; P=0.010$). Multiple linear regression analysis showed that the change of wall thickening in the infarct-adjacent zone was associated with the change of MD in the infarct-adjacent zone (the local wall) ($\beta=-0.180; 95\% CI=-0.292, -0.067$) and the change of mean HA in the remote zone (the distant wall) ($\beta=0.022; 95\% CI=0.004, 0.041$; Table 2; Figure 3A and 3B).

The sequential change of wall thickening in the remote zone was correlated inversely with the sequential change of MD in the infarct-adjacent zone ($r=-0.60; P=0.011$) and the remote zone ($r=-0.72; P=0.001$), and correlated with the sequential change of mean HA in the infarct-adjacent zone ($r=0.72; P=0.001$). Multiple linear regression analysis showed that the change of wall thickening in the remote zone was associated with the change of MD in the remote zone (the local wall) ($\beta=-0.153; 95\% CI=-0.296, -0.009$) and the change of mean HA in the infarct-adjacent zone (the distant wall) ($\beta=0.017; 95\% CI=0.002, 0.031$; Table 2; Figure 3C and 3D).

**Figure 2.** Viability zonal differences and sequential changes of microstructure of myocardium postinfarction. A, MD; B, FA; C, mean HA.
Normal Values and Reproducibility of DT-CMR in Healthy Control

The mean of MD of the global myocardium in the healthy controls (N=7) were 6.3±0.2×10⁻⁶ cm²/s in the first MR and 6.5±0.3×10⁻⁶ cm²/s in the repeated MR (P=0.32). The coefficient of variation was 4.5%. In the first and repeated MR, the mean of FA were 0.34±0.01 and 0.33±0.02 (P=0.54), respectively. The coefficient of variation was 7.0%. The mean of HA were 0.2±1.6° and 0.3±2.2° (P=0.58), respectively. The coefficient of variation was 11.2%. The RHF% were 26.6±3.2% and 28.2±2.8% (P=0.48), CF% were 52.3±4.6% and 49.7±4.3% (P=0.26), and LHF% were 20.6±1.1% and 22.0±1.8% (P=0.25), respectively.

Table 2. Correlation Between the Sequential Changes of Myocardial Macrostructure and Microstructure Postinfarction

<table>
<thead>
<tr>
<th>Microstructure</th>
<th>Infarct-Adjacent Zone</th>
<th>Remote Zone</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ΔWall Thickness, %</td>
<td>ΔWall Thickening, %</td>
</tr>
<tr>
<td>Infarct-adjacent zone</td>
<td></td>
<td></td>
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<tr>
<td>ΔMD</td>
<td>r = -0.35, P = 0.16</td>
<td>r = -0.70, P = 0.002</td>
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<tr>
<td>ΔFA</td>
<td>r = 0.41, P = 0.10</td>
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<td>Δmean HA</td>
<td>r = -0.07, P = 0.78</td>
<td>r = 0.41, P = 0.10</td>
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<tr>
<td>ΔLHF%</td>
<td>r = 0.33, P = 0.22</td>
<td>r = -0.32, P = 0.34</td>
</tr>
<tr>
<td>ΔCF%</td>
<td>r = -0.36, P = 0.15</td>
<td>r = 0.21, P = 0.62</td>
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<tr>
<td>ΔRHF%</td>
<td>r = 0.03, P = 0.90</td>
<td>r = 0.24, P = 0.74</td>
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<tr>
<td>Remote zone</td>
<td>ΔMD</td>
<td>r = -0.22, P = 0.40</td>
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<td>ΔFA</td>
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<td>r = -0.21, P = 0.42</td>
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<tr>
<td>Δmean HA</td>
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<td>ΔLHF%</td>
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<td>ΔCF%</td>
<td>r = -0.22, P = 0.40</td>
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<tr>
<td>ΔRHF%</td>
<td>r = 0.02, P = 0.95</td>
<td>r = 0.61, P = 0.010</td>
</tr>
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</table>

r values with P<0.05 are underlined. Δ indicates difference of measurement between recent MI and chronic MI.
Discussion

This follow-up study on the sequential changes of myocardial macrostructure and microstructure from recent MI to chronic MI supported and extended our previous observations. From recent MI to chronic MI, in macrostructure, the wall thickness and wall thickening showed progressive decrease in the infarct-adjacent zone and increase in the remote zone. In microstructure, there was global recovery of tissue integrity as reflected by the sequential decrease of MD. In correlation with functional changes, improvement of tissue integrity and increased right-handed helical reorientation correlated with recovery of the wall thickening.

MD indicates mean diffusivity of water molecules and reflects the redistribution of intracellular and extracellular space volumes.\textsuperscript{17-19} We postulate that the increase of MD in the remote region of recent MI to chronic MI results from initial increase in extracellular space due to cell lysis, followed by a decrease in the chronic MI as the healing process ensues.\textsuperscript{18,20} We believe our finding on sequential change of MD is reliable because (1) repeated measurements of MD of normal myocardium in our healthy control (6.3±0.2 to 6.5±0.3×10\textsuperscript{-6} cm\textsuperscript{2}/s, coefficient of variation=4.5%) were well reproducible; (2) our normal value of myocardial MD is close to a previous study (approximately 6.0±1.0×10\textsuperscript{-6} cm\textsuperscript{2}/s) in healthy volunteers using a more advanced cardiac DTI technique using a pair of bipolar diffusion gradient pulses, which is inherently insensitive to cardiac motion and strain; and (3) our normal values of myocardial MD is close to that of perfused myocardium of rabbits (7.2±0.7×10\textsuperscript{-6} cm\textsuperscript{2}/s).\textsuperscript{21} Therefore, in our chronic MI, MD in the remote zone (6.7±0.3×10\textsuperscript{-6} cm\textsuperscript{2}/s) was found to come closer to that of the normal myocardium, suggesting that in chronic MI, the tissue integrity of the remote zone was undergoing recovery toward the normal condition.

Our study found that in the recent MI (median, 21 days), the MD of the remote region was elevated (8.1±0.5×10\textsuperscript{-6} cm\textsuperscript{2}/s) when compared with the normal values (6.5±0.3×10\textsuperscript{-6} cm\textsuperscript{2}/s). Additionally, the decrease of MD over time (from 8.1±0.3×10\textsuperscript{-6} cm\textsuperscript{2}/s to 6.7±0.3×10\textsuperscript{-6} cm\textsuperscript{2}/s) was correlated with the improvement of wall thickening (Table 2). These findings suggest that in recent MI, myocardial edema is present even in the remote region. The edema subsides over time and is accompanied with the recovery of the regional wall thickening. Recent advance in T2WI cardiac MR could detect the

**Figure 3.** Scatter plots of correlation between changes of wall thickening and changes of microstructure. Scatter plots of correlation between changes of wall thickening in the infarct-adjacent zone versus change of MD in the infarct-adjacent zone (A) and change of mean HA in the remote zone (B) are shown, as well as correlation of changes of wall thickening in the remote zone versus change of MD in the remote zone (C) and change of mean HA in the infarct-adjacent zone (D).
presence of myocardial edema. It was reported that the area of edema is generally larger than the myocardial necrosis and may extend to the adjacent region. In our study, we found MD progressively increased from remote to infarct myocardium, suggesting that MD might be a sensitive marker for myocardial edema and could detect the subtle increase of edema in the remote region. Our finding is not consistent with an ex vivo DT-CMR study on a porcine model by Wu et al in which no significant difference in MD was found when compared with the control group in the adjacent and remote regions. The discrepancy may be related to the dehydration procedure performed in formalin fixation, which may reduce the myocardial water content and consequently MD.

FA is a sensitive marker for microstructure integrity of neuronal axons and has been validated histologically. However, the validity of FA in representing integrity of myocardial fibers is not as clear as neuronal axons. This may be due to the fact that the volume fraction of the extracellular space in the myocardium varies spatially, leading to heterogeneity of FA over the ventricular walls. As Jiang et al demonstrated in the sheep myocardium, FA varies transmurally; it remained relatively constant from the epicardium to the midwall and then decreased steadily toward the endocardium. The relative low FA values in the inner wall may confound the decrease of FA due to myocardial ischemia, which is predominantly located in the subendocardium.

As shown in Figure 3 and Table 2, the recovery of wall thickening in the infarct-adjacent zone was associated with the sequential changes of MD in the infarct-adjacent zone and mean HA in the remote zone. Likewise, the recovery of wall thickening in the remote zone was associated with the sequential changes of MD in the remote zone and mean HA in the infarct-adjacent zone. The above findings suggested that microstructural improvement of local tissue integrity (decrease of MD) and remodeling of distant fiber architecture (ie, more right-handed helical reorientation) might both associate with the functional improvement of wall thickening.

The current study has made 2 important observations regarding the increase of RHF% in the remote zone of myocardium postinfarction. First, the sequential increase of wall thickness in the remote zone had significantly correlated with the sequential increase of RHF% (r = 0.66; P = 0.005); second, improvement of wall thickening in the infarct-adjacent zone was correlated with the increase of mean HA in the remote zone, which was mainly due to increase of RHF% (r = 0.61; P = 0.010; Table 2). The increase of RHF% presented a preferential increase of subendocardial fiber, which has also been observed in the LV after heart failure or exercise-training as a stress adaptive response.

Our finding of fiber architecture adaptation after MI is at variance with those observed by Chen et al at ex vivo animal study of DT-CMR post-MI. We found it difficult to apply direct comparison between Chen’s versus our results (see online-only Data Supplement). In brief, species-distinct myocardial healing and remodeling do exist; specimen preparation-relevant factors such as permanent ligation versus reperfusion therapy and ex vivo versus in vivo measurement may affect; and DT-CMR relevant factors such as spatial resolution and anisotropy of voxel dimensions may all contribute to the discrepancy. Likewise, there is variance between results by Geerts et al and Chen et al.

The LV asynchrony post-MI may have potential influence on the measurement of microstructure by DT-CMR. With calculation and simulation of the potential effects in our cases, we found that asynchrony has no significant impact on our conclusion (see online-only Data Supplement).

**Study Limitation**

In this study, only a half of the patients from the initial study were enrolled because of the inclusion and exclusion criteria used in patient selection, as described in the Patient section. The observation was made in a group of patients with stable hemodynamic conditions post-MI. Therefore, the conclusions drawn from this study might not be applicable to patients with poor outcome of functional recovery. Our scan range was limited to the middle ventricular volume to constrain the scan time. In addition, we did not conduct spatial correlation analysis on the slice-level measurements, therefore might loss of power and possibly bias in comparison with approaches that use each individual slice measurements accounting for the within-heart correlation of macrostructures and microstructures. Lastly, several borderline results, such as sequential change of wall thickening, MD and FA, may be hindered by type-II error due to small case number.

**Conclusions**

We used DT-CMR to investigate the sequential changes of myocardial macrostructure and microstructure from recent MI to chronic MI. Microstructure improvement of tissue integrity and fiber architecture remodeling toward right-handed helical reorientation might both associate with improvement of wall thickening in macrostructure. This observation may shed light on the management involving restoration of normal scaffold of fiber architecture in myocardium postinfarction.

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**Disclosures**

None.

**References**


**CLINICAL PERSPECTIVE**

Postinfarction late remodeling involves the left ventricle globally and is associated with time-dependent dilatation, distortion of ventricular shape, rearrangement of fiber architecture, and mural hypertrophy. Clearly, there is a great need for, and utility in, the in vivo acquisition of a wealth of cardiac microstructures, such as geometry, fiber and sheet orientation, and cell populations, to improve our ability to design strategies for effective restoration of myocardium postinfarction. This study investigated the sequential changes of myocardial microstructure from recent myocardial infarction to chronic myocardial infarction and correlated it with the sequential changes of the left ventricular wall thickness and thickening. Wall thickness and wall thickening decreased sequentially in the infarct-adjacent zone and increased in the remote zone. In microstructure, there was improvement of tissue integrity, reflected by decreased mean diffusivity. This improvement was found to be associated with the improvement of the thickening of the local wall. Fiber architecture adaptation showed more right-handed helical reorientation (increased subendocardial fiber proportion) and was correlated with improvement of the thickening of the remote wall. The observed interplay between myocardial microstructure and the left ventricular wall structure and function may shed light on the biomechanics behind the process of postinfarction remodeling and might be helpful in the management involving restoration of normal scaffold of fiber architecture in myocardium postinfarction.
Sequential Changes of Myocardial Microstructure in Patients Postmyocardial Infarction by Diffusion-Tensor Cardiac MR: Correlation With Left Ventricular Structure and Function
Ming-Ting Wu, Mao-Yuan M. Su, Yi-Luan Huang, Kuan-Rau Chiou, Pinchen Yang, Huay-Ben Pan, Timothy G. Reese, Van J. Wedeen and Wen-Yih I. Tseng

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Supplemental Methods: Methodology comparisons with animal ex vivo study,

While the present study is the first DT-MRI of human beating heart post MI, our finding of fiber architecture adaptation after MI is at variance with those observed by Chen et al, who reported the first, and so far the only one, animal study of DT-MRI post MI.¹ In formalin-fixed rat hearts, they also found that trace ADC increased and relative anisotropy (equivalent to FA) decreased in the infarct zone, however, the inclination angle (equivalent to our helix angle) of fiber architecture was relatively preserved except with greater angular deviation. Multiple variations between Chen’s study and our present study make direct comparison inapplicable. First, different biological models were used. Chen et al. performed permanent total ligation over the left anterior descending artery without reperfusion uniformly in every rat, and observed the fiber architecture of formalin-fixed myocardium at 4 weeks after acute MI. In contrast, we observed the living human heart at the median of 26 days after acute MI in patients with different severity of occlusion at a variety of culprit vessels and most of them received reperfusion treatment. The impacts were complex, for example, it has been reported that the coronary anatomy and myocardial infarction consequent to ligation are distinct among different species² the rate of collagen deposition after MI may also vary significantly among different species³ and reperfusion or not has different effects on healing of MI.⁴ Second, different DT-MRI variables were used. Chen et al acquired DT-MRI with extremely anisotropic voxel dimensions (1: 1: 12.8) and we used less anisotropic voxel dimensions (1: 1: 4.3). It should be noted that measurement of FA and fiber helix angle by DT-MRI is the more isotropy of voxels the more accuracy of the results.⁵ Although ours spatial resolution is relatively lower than Chen’s, it is equivalent to that used in brain DTI and have at least 6 transmural voxels on average across the infarct zone so as sufficient to reflect the fiber architecture remodelling post MI. We believe that all of these factors attributed to the discrepancy between Chen’s findings and ours. Just like the discrepancy between Geerts et al.⁶ and Chen et al.,⁵ these differences in species, methods, and definitions prevent strict comparisons between the two data sets.¹
References:


Supplemental Methods: Simulation of potential effects of asynchrony on myocardial diffusion measurement

In this study, we used double-gated stimulated-echo echo-planar image to acquire DT-CMR, and acquired diffusion images at the “sweet spot” at mid systole when the myocardial strain over a cardiac cycle was averaged to zero. In the presence of asynchrony between the infract zone and remote zone, there may be a time lag of the sweet spots in two zones and produce error in diffusion measurement. As the timing of diffusion encoding deviates from the true “sweet spot”, the local myocardial strains act on local fibers, causing deviation of fiber helix angles. The helix angles could increase in some fibers while decrease in other fibers. As the timing of diffusion encoding deviates from the “sweet spot”, the mean and variance of the deviation angles increases with time. This effect could affect the precision and accuracy of the helix angle measurement of individual fibers.

To estimate the potential effects of asynchrony on diffusion measurement, simulation was performed based on a set of normal data which contained co-registered DTI and strain-rate MRI. The pixels in the co-registered DTI and strain-rate MRI were located in the LV at the mid-ventricular short-axis view. The deviation from the sweet spot and the consequent deviations of fiber helix angle was estimated by the relationship between the observed diffusion tensor acquired at time $t$, $D_{\text{obs}}(t)$, and the diffusion tensor acquired at the sweet spot $t'$, $D_{\text{obs}}(t')$, i.e., $D_{\text{obs}}(t) - D_{\text{obs}}(t') = S(t) D_0 + D_0 S(t)$. Based on the MASS analysis of the cine fast gradient echo images, the time point of maximal wall thickening of the infarct-adjacent zone and the remote zone were determined. The absolute difference of the two time points was examined. In the recent MI, the time point at maximal wall motion was 324±27 ms after R-wave in the infarct-adjacent zone and 330±23 ms in the remote zone, with an asynchrony interval of median = 21 ms [range 0 to 75 ms]. In the chronic MI, the time point at maximal wall motion was 378 ±13 ms in the infarct-adjacent zone and 382 ±12 ms in the remote zone, with an asynchrony
interval of median = 38 ms [range 0-73 ms]. The asynchrony intervals we calculated were comparable to the others’ observation.3

In this study, mean helix angles were computed in the infarct-adjacent zone and the remote zone for each subject, the mean helix angles for each zones were then averaged over all the subjects. Our simulation results showed that given the range of asynchrony in our results, 0-75 msec, the mean HA in the infarct-adjacent zone was estimated to be approximately 0-4 degree (Table). Such amount of deviation is rather small as compared with the observed difference between the infarct-adjacent zone and remote zone (around 23° to 26°). The impact of this deviation on the change in the percentage of right-handed and left handed fiber population was further assessed. The results showed that as the deviation time increased from 0 ms to 100 ms, the right-handed fiber population increased from 27.5% to 31.4%, and the left-handed fiber population decreased form 21.2% to 17.4% (Table). Despite this potential error, we still find distinguishable difference in the infarct-adjacent zone as compared to the remote zone. The infarct-adjacent zone showed less RHF% (14% vs. 36% in the remote zone) and more LHF% (28% vs. 13% in the remote zone) (Table 2 in the manuscript).

**Supplemental Table**

Simulation results of deviation from the sweet spot and the consequent changes of fiber helix angle, right-handed and left-handed fiber populations

<table>
<thead>
<tr>
<th>Δt (ms)</th>
<th>0</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔHA (deg.)</td>
<td>0</td>
<td>1.1±1.5</td>
<td>2.3±2.8</td>
<td>3.8±5.7</td>
<td>5.6±8.3</td>
</tr>
<tr>
<td>RHF%</td>
<td>27.5</td>
<td>28.8</td>
<td>30.5</td>
<td>32.2</td>
<td>31.4</td>
</tr>
<tr>
<td>LHF%</td>
<td>21.2</td>
<td>20.8</td>
<td>19.5</td>
<td>18.2</td>
<td>17.4</td>
</tr>
</tbody>
</table>

References:
