Cardiac Diffusion MRI Without Motion Effects

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We present a method for diffusion tensor MRI in the beating heart that is insensitive to cardiac motion and strain. Using a stimulated echo pulse sequence with two electrocardiogram (ECG) triggers, diffusion-encoding bipolar gradient pulses are applied at identical phases in consecutive cardiac cycles. In this experiment, diffusion is encoded at a single phase in the cardiac cycle of less than 30 ms in duration. This encoding produces no phase shifts for periodic motion and is independent of intervening strains. Studies in a gel phantom with cyclic deformation confirm that by using this sequence we can map the diffusion tensor free of effects of cyclic motion. In normal human subjects, myocardial diffusion eigenvalues measured with the present method showed no significant change between acquisitions encoded at maximum contractile velocity (peak) vs. at myocardial standstill (end-systole), demonstrating motion independence of in vivo diffusion measurements. Diffusion tensor images acquired with the present method agree with registered data acquired with a previous cardiac diffusion MRI method that was shown to be valid in the normal heart, strongly supporting the validity of MRI diffusion measurement in the beating heart. Myocardial sheet and fiber dynamics measured during systole showed that normal human myocardial sheet orientations tilt toward the radial during systole, and fiber orientations tilt toward the longitudinal, in qualitative agreement with previous invasive studies in canines. These results demonstrate the technique’s ability to measure myocardial diffusion accurately at any point in the cardiac cycle free of measurable motion effect, as if the heart were frozen at the point of acquisition. Magn Reson Med 48:105–114, 2002. © 2002 Wiley-Liss, Inc.

Key words: MRI; diffusion; myocardium; strain; motion effect; myocardial structure; dynamics

Diffusion MRI provides a noninvasive window into tissue architecture (1–8). In the heart, myocardial structure and function are intimately linked and can change dramatically in disease. Accordingly, diffusion MRI methods have been developed to map myocardial architecture in vivo (1,3–5,8). Initially, methods were devised that, by encoding diffusion over an exact cardiac cycle, sought insensitivity to gross cardiac motion (1). It subsequently was found that such diffusion encodings interact with myocardial strain, and methods were described to overcome this effect by measuring the history of myocardial strains (3–5,8). A comprehensive measurement of cardiac strain can be challenging, but, more germanely, it leaves the dependent diffusion measurements open to question, to the extent that they may be influenced by unrecognized cardiac motion or some other unanticipated mechanism.

This work presents a new method for diffusion MRI in the beating heart which encodes diffusion at a single cardiac phase. We demonstrate that this method fully addresses the problem of motion sensitivity of diffusion MRI in the beating heart.

METHODS

Experimental Design

To encode diffusion in a single cardiac phase in the beating heart, we use a bipolar gradient pulse of less than 30 ms in duration. The two gradient lobes (encoding and de-encoding gradient pulses) in the bipolar pulse are identical but are opposite in sign, which limits the diffusion sensitivity to the interval of the bipolar pulse. Thus, the applied bipolar pulse effectively encodes diffusion at a single cardiac phase. This bipolar pulse requires flow compensation (1). To accomplish this, after phase reversal we apply an identical bipolar gradient pulse at the identical phase of the next cardiac cycle, using a stimulated echo with two electrocardiogram (ECG) triggers (Fig. 1a). This sequence is perfectly flow-compensated for periodic motion, and the net diffusion sensitivity is the sum of the contributions of the two bipolar gradients.

Previously, a similar alternative method was proposed using unipolar pulses (1) (Fig. 1b). This “unipolar method,” while free of phase sensitivity to motion of cardiac periodicity, remains sensitive to material strains over the cardiac cycle. In this method, the diffusion encoding persists over the entire cardiac cycle that intervenes between the encoding and de-encoding gradient pulses. At any time during this period, material strain physically stretches the applied spatial modulation of spin phase; thus, the encoding yields diffusion contrast that indicates an observed diffusion tensor that is in general different from that which would have been observed had the material remained stationary (4). Given this effect, methods were proposed to accurately determine the true underlying diffusion, first by calculation based on MRI of the full myocardial strain history (3), and then in the normal heart by locating special cardiac delays (“sweet spots”) wherein strain effects cancel (5). The bipolar method described herein should be free of this effect, because it has no diffusion sensitivity during the intervening cardiac cycle when strain occurs.

This section validates the new method in two ways. First, we show in a phantom with cyclic motion that diffusion measurements with the bipolar encoding are in...
bipolar methods in a phantom with cyclic strain. The first is a cylinder of aqueous gelatin 12 cm high × 12 cm in radius, the top face of which is cyclically indented along the cylinder axis to a depth of 2 cm by a motorized plunger at a constant rate of one indentation per 750 ms.

Experiments were performed on a 1.5-T GE Signa MR imager. Images of the gelatin phantom at different phases in the deformation cycle were acquired using the uni- and bipolar encoding techniques. Diffusion encoding used gradients \( \mathbf{G} \) directed to non-opposed edge centers of a cube ([1,1,1],[0,1,1],[1,0,1]) of intensity \( |\mathbf{G}_1| = 3.1 \text{ mT m}^{-1} \) for the unipolar method, and \( |\mathbf{G}_p| = 40 \text{ mT m}^{-1} \) for the bipolar method. Pulse offset \( \Delta_U = 750 \text{ ms} \) and duration \( \delta_U = 26.2 \text{ ms} \) in the unipolar case, and \( \Delta_B = \delta_B = 13.2 \text{ ms} \) in the bipolar case (see Fig. 1), furnishing equal diffusion sensitivities of \( b \approx 350 \text{ s mm}^{-2} \) in both cases. The uni- and bipolar diffusion sensitivities are given by

\[
\begin{align*}
\mathbf{b}_U &= |\mathbf{k}_U|^2 (\Delta_U - \delta_U/3) \quad [1a] \\
\mathbf{b}_B &= 4/3|\mathbf{k}_B|^2\delta_B \quad [1b]
\end{align*}
\]

respectively, where \( \mathbf{k}_i = 2\pi\gamma\delta\mathbf{G}_i \) is the spatial modulation vector in each case, where \( i = \{U,B\} \) and \( \gamma \) is the proton gyromagnetic ratio. Spatial encoding used single-shot EPI with 3-mm isotropic resolution. Equal echo times (TE = 82 ms) were used in both cases. Diffusion tensor MRI movies were acquired with 50-ms progressive delays for a single slice that contains the phantom axis. Registered phase-contrast MRI movies of 2D strain rates were also acquired (3,9).

After data acquisition, the diffusion tensor images at each time frame were computed by linear inversion of the relations for the image attenuations in the uni- and bipolar experiments \( I_U/I_0 \) and \( I_B/I_0 \), respectively:

\[
-\log(I_U/I_0) = (\Delta_U - \delta_U/3)|\mathbf{k}_U|^2D_{obs} \mathbf{k}_U \quad [2a]
\]

\[
-\log(I_B/I_0) = 4/3\delta_B|\mathbf{k}_B|^2D_{obs} \mathbf{k}_B \quad [2b]
\]

where \( I_U \) and \( I_B \) represent diffusion-attenuated images by the uni- and bipolar methods, \( I_0 \) represents unattenuated image, and \( D_{obs} \) is the measured diffusion tensor (10). The corresponding strain rate images were also calculated. To quantify the changes in the observed diffusivity, we examined the radial component \( D_{obs} \) of the observed diffusion tensor \( D_{obs} \). \( D_{obs} \) is the radial unit vector, with polar origin at plunger contact (Fig. 2, top center).

As previously shown (5), for the unipolar method, if we let \( \mathbf{S}(\tau) \) be the strain at time \( \tau \) relative to time \( t \), and \( <\ldots> = \Delta^{-1}\int_{\tau} <\ldots> \text{ d}t \) denote the time-average over one cardiac cycle \( \Delta \), then the measured diffusivity \( D_{obs} \) is related to the true intrinsic diffusivity \( D_0 \) by

\[
D_{obs}(t) = D_0 - <\mathbf{S}_t > D_0 - D_0 <\mathbf{S}_t > \quad [3]
\]

where strains are computed relative to the configuration at the time of measurement. For the radial component, Eq. [3] becomes
but that in the unipolar case variations of should be constant in space and time. To measure the motion- and strain-independent, the observed diffusivity unipolar method will have both spatial and time variations where \( \sigma_{r,t} \) standard deviation (SD) using the uni- and bipolar pulse sequences. The top image is the FIG. 2. Diffusion MRI of a cyclically deformed gel phantom acquired respectively. The magnitudes of the pixel over the deformation cycle acquired with equal diffusion sen-

indicates the region that has apparent strain effect, which is revealed by large arrow in a. In b, such strain effect approaches the noise level.

\[
D_{\text{obs}}(t) = (1 - 2 < S_{r,t}>) D_{r,0} \\
\approx (1 - 2 f(t) S_{r,t}^{\text{max}}) D_{r,0} \\
\text{[4]}
\]

where \( S_{r,t}^{\text{max}} \) is the map of peak radial strain and \( f(t) \) is a scalar function describing the time dependence of \( S \) (11).

Because the diffusivity of the gel phantom is uniform and is also unaffected by the strain (4), i.e., \( D_{r,0} \) is constant, the above equation gives that the \( D_{r,\text{obs}} \) measured by the unipolar method is dependent on \( S_{r,t} > \). Since \( S_{r,t} > \) varies with \( t \) and location, it is expected that \( D_{r,\text{obs}} \) of the unipolar method will have both spatial and time variations through the deformation cycle. If the bipolar method is motion- and strain-independent, the observed diffusivity should be constant in space and time. To measure the variations of \( D_{r,\text{obs}} \), we compute an image representing the standard deviation (SD) \( \sigma \) of the time-series \( D_{r,\text{obs}}(x) \) at each location \( x \)

\[
\sigma[D_{r,\text{obs}}(x,t)] = \sqrt{ \left[ D_{r,\text{obs}}(x,t) - < D_{r,\text{obs}}(x,t) > \right]^2 }^{1/2}. \text{[5]}
\]

We hypothesize that in the bipolar case \( \sigma[D_{r,\text{obs}}(x, t)] \approx 0 \) but that in the unipolar case \( \sigma[D_{r,\text{obs}}(x, t)] \neq 0 \), and in particular

\[
\sigma[D_{r,\text{obs}}(x,t)] \approx S_{r,t}^{\text{max}}. \text{[6]}
\]

Validation In Vivo

Myocardial Diffusion Eigenvalues During Systole

Using the bipolar method, we measured myocardial diffusion eigenvalues at different phases in systole on a normal human subject, and compared the observed values at moving phases (during systole) with that at the standstill phase (end-systole) to examine the cardiac motion effect.

After providing written informed consent, which was approved by the hospital human studies committee, the subject was instructed to use synchronized breathing to suppress respiration motion in the diffusion studies. ECG R-wave triggering was used for data acquisition. After a midventricular short-axis slice was located, the standstill phase at end-systole was found at an ECG trigger delay of approximately 325 ms by examining myocardial velocity phase maps at multiple points throughout the cardiac cycle. Diffusion images at six phases from early-systole (trigger delay = 75 ms) to end-systole (trigger delay = 325 ms) in 50-ms time steps were then acquired using single-shot EPI with a spatial resolution of \( 4 \times 4 \times 12 \text{ mm} \). The diffusion-encoding gradient intensity used was \( |G_B| = 40 \text{ mT m}^{-1} \), and pulse duration \( \delta_B = 13.2 \text{ ms} \), furnishing a diffusion sensitivity of \( b \approx 350 \text{ s mm}^{-2} \). TE = 82 ms and TR = 4 R-R intervals were used in all acquisitions. The heart rate of the subject was stable during the experiment. The total imaging time per study was under 10 min. After the quality of acquired images was assured by examining both the magnitude and phase images, myocardial diffusion eigenvalues were calculated at each image pixel. The mean diffusion eigenvalues of the left ventricle (LV) (with papillary muscle excluded) were then computed at each phase for comparison.

If the bipolar method is insensitive to the cardiac motion effect, i.e., there are little or no hidden motion effects on the measurements, we expect that the observed diffusion eigenvalues should show little or no differences between the moving phases (during systole) and the stand-still phase (end-systole).

Agreement Between the Bipolar Method and the Unipolar Sweet Spot Method

As previously described (5), the unipolar method provides an accurate map of the myocardial diffusion tensor field in the normal heart at times \( t \) (the sweet spots) wherein the strain effect is canceled. To validate the overall accuracy of the unipolar sweet spot method, and to demonstrate the accuracy of the bipolar method for in vivo studies (especially in structural measurements), we compared the bipolar method and the unipolar method at several points in the cardiac cycle, including the sweet spot.

The experiment was performed on a healthy human subject whose average heart rate was 64 beats/min during the experiment. Synchronized breathing and ECG R-wave triggering were used for data acquisition as in previous studies. After a midventricular short-axis slice was located, the diffusion images were spatially encoded using single-shot EPI with a spatial resolution of \( 4 \times 4 \times 12 \text{ mm} \). Registered diffusion images measured by the uni- and bipolar methods at four points in the cardiac cycle (trigger delay = 80 ms, 160 ms (sweet spot), 240 ms, and 320 ms)
were then obtained. The diffusion-encoding gradient intensity used was $|G_U| = 2.8$ mT m$^{-1}$ for the unipolar method, and $|G_B| = 40$ mT m$^{-1}$ for the bipolar method. Pulse durations $\delta_u = 26$ ms and $\delta_b = 13.2$ ms. With a heart rate of 64 beats/min, these parameters furnish an equal diffusion sensitivity $b \approx 350$ s mm$^{-2}$ for both methods. TE = 82 ms and TR = 4 R-R intervals were used for both cases, and the total imaging time per study was under 10 min for both methods.

After registered uni- and bipolar diffusion images were obtained, image quality was assured by examining both the magnitude and the phase images. The diffusion tensors were then calculated at each image. Pixels of the LV (with papillary muscle excluded) were used for comparison. To validate the overall accuracy of the sweet spot method, we estimated the mean diffusion eigenvalues measured by the bipolar method and the sweet spot method to show that the sweet spot method is insensitive to the cardiac motion effect. To demonstrate the accuracy of the bipolar method in measuring in vivo myocardial structures, we compared observed diffusion tensors $\mathbf{D}$ and eigenvectors of $\mathbf{D}$ at each pair of unipolar-bipolar registered pixels at all four cardiac phases. The $\mathbf{D}$ were compared by representing the tensors as vectors $\mathbf{d} = \{D_{11}, D_{22}, D_{33}, D_{12}, D_{13}, D_{23}\}$, where $D_{ij}$ are tensor components. The tensor difference $T_d$ between the unipolar and bipolar methods were then calculated as $T_d = |\mathbf{d}_u - \mathbf{d}_b|^2$, where $\mathbf{d}_u$ and $\mathbf{d}_b$ are tensor data measured by the unipolar and the bipolar method, respectively. The eigenvectors of $\mathbf{D}$ are indicators of the myocardial fiber and sheet structure (1–8), and were compared by representing the tensors and eigenvectors calculated by these two half data sets and comparing differences between the same set of diffusion attenuation images into two half data sets and comparing differences between the tensors and eigenvectors calculated by these two half data sets. The differences by the noise for the full data sets were then estimated by using the noise reduction relation between the half and full data sets.

If both the bipolar method and the unipolar sweet spot method are accurate and insensitive to the cardiac motion effect, we expect that the bipolar method and the unipolar method should agree at the sweet spot, where the measurement differences should be close to the noise level. We also expect that the unipolar and bipolar methods should disagree (differences $>$ noise level) at other points at which the bipolar method still holds accuracy while the unipolar method is disrupted by the strain effect.

### Dynamics of Myocardial Fibers and Sheets During Systole

As previously shown (1–8), the eigenvectors of the myocardial diffusion tensor are indicators of the myocardial structure: the first eigenvector corresponds to the fiber vector, the second eigenvector corresponds to the sheet vector, and the third eigenvector corresponds to the sheet normal vector. Using the bipolar method to measure myocardial diffusion tensors at different cardiac phases, we examined the myocardial sheet and fiber dynamics during contraction in a normal human heart, and compared the results with previous invasive studies on canines.

With the same experimental setup described for the methods for in vivo validation, we acquired diffusion images by the bipolar method at three points (trigger delay = 80 ms (early-systole), 200 ms (mid-systole), and 320 ms (end-systole)) in the cardiac cycle. Sheet and fiber dynamics during systole were then studied by examining the histograms of sheet angle $\theta_S$ and helix angle $\theta_H$ at these points. At each pixel, let $\mathbf{d}_1$, $\mathbf{d}_2$ be the first and second eigenvectors, respectively, of the diffusion tensor; $\mathbf{c}$ be the circumferential unit vector, defined as the normalized gradient of the polar angle about the LV centroid; and $\mathbf{r}$ be the radial unit vector with origin at the LV centroid. The fiber vector $\mathbf{f}$, sheet vector $\mathbf{s}$, and sheet normal vector $\mathbf{n}$ are defined as

$$
\mathbf{f} = \text{sign}(\mathbf{d}_1 \cdot \mathbf{c})\mathbf{d}_1,
\mathbf{s} = \text{sign}(\mathbf{d}_1 \cdot \mathbf{r})\mathbf{d}_2,
\mathbf{n} = \mathbf{f} \times \mathbf{s}.
$$

Let $\mathbf{f}_\perp$ be the unit projection of $\mathbf{f}$ onto the epicardium tangent plane, i.e., the circumferential-longitudinal ($c\cdot l$) plane, where $\mathbf{l} = \mathbf{r} \times \mathbf{c}$, and $\mathbf{r}_\perp$ be the unit projection of $\mathbf{r}$ onto the plane formed by $\mathbf{s}$ and $\mathbf{n}$. The sheet angle $\theta_S$ is then defined as the angle between the sheet normal vector $\mathbf{n}$ and the radial projection vector $\mathbf{r}_\perp$.

$$
\theta_S = \text{sign}(\mathbf{r}_\perp \cdot \mathbf{n})\text{arccos}(|\mathbf{r}_\perp \cdot \mathbf{n}|).
$$

The helix angle $\theta_H$ is defined as the angle between the circumferential vector $\mathbf{c}$ and the fiber projection vector $\mathbf{f}_\perp$.

$$
\theta_H = \text{sign}(\mathbf{f}_\perp \cdot \mathbf{c})\text{arccos}(|\mathbf{f}_\perp \cdot \mathbf{c}|).
$$

The slice examined is at left midventricle (with papillary muscle excluded).

### RESULTS

#### Validation Ex Vivo

Figure 2 shows the diffusion MRI of the gel phantom acquired using the uni- and bipolar pulse sequences; the magnitude image is at the top of the figure, and the images of observed SDs $\sigma$ of radial diffusivities over the deformation cycle for uni- and bipolar sequences with equal diffusion sensitivities are shown at the center and bottom, respectively.

In a wedge-shaped ROI beneath the plunger, a region of relatively high strain, it was found that principle strains $S$ and strain-rates $dS/dt$ have maxima $\max(S) = 0.3$ and $\max(dS/dt) = 2 \pm 1$ s$^{-1}$, similar in size to normal human myocardial values. For individual diffusivity maps measured during the deformation cycle, we found that those of the unipolar experiments show significant spatial variations due to the strain effect. However, in the bipolar experiments the spatial variations of observed radial dif-
In Fig. 2, we computed the SDs of Dr,obs variability of 5–10% (around 5% in the current experiments). In Fig. 2, we computed the SDs σ of Dr,obs over the deformation cycle (Eq. [5]). In the unipolar experiment, the SDs σ of Dr,obs are large (Fig. 2a), with σ(Dr,obs) as great as 50% of the mean diffusion near the plunger. By contrast, the bipolar experiment shows a σ(Dr,obs) of at most 5% of the mean diffusion (Fig. 2b), representing a 10-fold reduction of the strain effect.

Validation In Vivo
Myocardial Diffusion Eigenvalues During Systole

Figure 3 shows the mean diffusion eigenvalues during contraction at 50-ms time steps on a normal human subject. The eigenvalues are nearly constant during contraction, with no statistically significant differences (P < 0.05) from early- to mid-systole (75–175-ms delay after R-wave), or from mid- to end-systole (175–325-ms delay). For the whole range from early- to end-systole, the diffusion eigenvalues show a statistically significant change of 5–10% (P < 0.05).

Agreement In Vivo Between the Bipolar Method and the Unipolar Sweet Spot Method

Figure 4 shows the mean myocardial diffusion eigenvalues measured by the bipolar method and the sweet spot method during contraction on the subject in study, and also the mean diffusion eigenvalues of six normal subjects previously measured by the sweet spot method. The intrasubject results show that the bipolar method agrees with the sweet spot method. The intersubject results show that, within the experimental uncertainties, the myocardial diffusion eigenvalues of different subjects are in a similar range.

Table 1 compares the measurement results of the tensor field by the unipolar method and the bipolar methods at ECG R-wave trigger delays of 80 ms, 160 ms (sweet spot), 240 ms, and 320 ms. We see that the two methods agree at the sweet spot, where the differences are at the noise level, and disagree at other points where the unipolar method is inaccurate.

Dynamics of Myocardial Fibers and Sheets

Figure 5 shows the myocardial structure measured by the bipolar method at ECG R-wave trigger delays of 80 ms, 200 ms, and 320 ms. The images show a classic distribution of fiber orientations from the epicardium to the endocardium. Examining through the time course shows that the sheets become more radially oriented during contraction, and the sheets in the septum and the freewall tilt in parallel in this period. Fiber helix angle changes during contraction can not be observed directly from the images, but are revealed in the histogram analysis in Fig. 6.

Figure 6a shows the histograms of the sheet angle θs at ECG R-wave trigger delays of 80 ms (early-systole), 200 ms (mid-systole), and 320 ms (end-systole). From this histogram “movie” we see that the histogram becomes broader (from 80 ms (sheet angle SD = 4° ± 3° (CI)) to 320 ms (sheet angle SD = 41° ± 4°)), indicating that the sheets become more radially oriented during contraction. This result is in qualitative agreement with that obtained in canine hearts by LeGrice et al. (12), who found that the flipping of the myocardial sheet to the radial direction (sheet shear) contributes to systolic wall thickening.

Figure 6b shows the histograms of the helix angle θf during contraction. We see that the histogram becomes broader (from 80 ms (helix angle SD = 36° ± 4°) to 320 ms
(helix angle SD = 44° ± 5°), indicating that the fibers become more longitudinally oriented during this period. This result is in qualitative agreement with that from a study on canine hearts by Streeter et al. (13), who found that the myocardial fibers of the LV become more longitudinally oriented during systole.

**DISCUSSION**

**Experimental Design**

Cardiac motion is the central obstacle to in vivo MRI of myocardial diffusion. An effective MRI methodology should be able to image myocardial diffusion without motion effects, i.e., it should be able to measure myocardial diffusion as if the heart were arrested at the time of measurement. To realize this, the desired method should satisfy two conditions: 1) It should encode diffusion in a very short time compared to the heart contraction time, so the myocardium is nearly immobilized at the time of imaging. 2) There should be no diffusion sensitivity outside the time of encoding, so that the diffusion measurement will not be affected by motion effects from times outside the diffusion encoding period. The bipolar diffusion-encoding gradient is designed for this purpose. The <30-ms pulse duration satisfies condition 1, and the bipolar gradient pulse, which limits the diffusion encoding to within the duration of the diffusion-encoding pulses, satisfies condition 2. Thus, the use of bipolar diffusion-encoding pulses effectively encodes diffusion at a single cardiac phase and eliminates motion effects from outside the diffusion-encoding period.

However, satisfying these two conditions is not sufficient to solve the problem. The <30-ms pulse duration is short compared to the contraction time, but is long enough for the cardiac gross motion to create phase shifts inside each voxel that may cause loss of signal. Hence “flow compensation” is needed. Traditional flow compensation would use a second bipolar pulse immediately following

<table>
<thead>
<tr>
<th>Time</th>
<th>Tensor ($T_d$) ($10^{-12}$ cm/s$^2$)</th>
<th>$T_d/T_d$ (noise)</th>
<th>1st eigenvector ($\theta_1$)</th>
<th>2nd eigenvector ($\theta_2$)</th>
<th>3rd eigenvector ($\theta_3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 ms</td>
<td>7.5 ± 0.6</td>
<td>3.75</td>
<td>16.0° ± 1.8°</td>
<td>23.5° ± 2.7°</td>
<td>19.1° ± 1.7°</td>
</tr>
<tr>
<td>160 ms</td>
<td>2.1 ± 0.3</td>
<td>1.05</td>
<td>9.0° ± 1.1°</td>
<td>13.8° ± 1.4°</td>
<td>10.3° ± 1.2°</td>
</tr>
<tr>
<td>240 ms</td>
<td>10.3 ± 1.5</td>
<td>5.15</td>
<td>15.6° ± 1.9°</td>
<td>28.7° ± 3.3°</td>
<td>24.6° ± 3.5°</td>
</tr>
<tr>
<td>320 ms</td>
<td>13.0 ± 1.9</td>
<td>6.50</td>
<td>21.5° ± 2.7°</td>
<td>39.8° ± 3.8°</td>
<td>34.3° ± 4.1°</td>
</tr>
<tr>
<td>Noise estimate</td>
<td>2.0 ± 0.3</td>
<td>1.00</td>
<td>8.9° ± 1.1°</td>
<td>13.9° ± 1.3°</td>
<td>10.4° ± 1.2°</td>
</tr>
</tbody>
</table>

*Sweet spot in bold (160 ms).

FIG. 5. Fiber architecture of a left midventricle short-axis slice during contraction measured by the bipolar method at ECG R-wave trigger delay of (a) 80 ms, (b) 200 ms, and (c) 320 ms. The fiber architectures are represented by colored boxes, with fiber $f$, sheet $s$, sheet normal $n$ vectors perpendicular to red, green, and blue-colored surfaces, respectively, viewed from above the slice. The anterior wall is at the top, and the septum is at the left in each image. The images show classic distribution of fiber orientations from epicardium to endocardium. The first column of images clearly show that the sheets become more radially oriented during contraction (the sheet axis becomes more perpendicular to the viewing axis in images a–c). Note also that the sheets in the septum and the freewall tilt in parallel during contraction.
the first with reversed sign (+−, −+) to reverse velocity phase shifts, but this solution is unsatisfactory in the heart because of non-constant velocity over the required time intervals. To address this, we used a stimulated echo sequence with two ECG triggers to put the velocity compensation at identical phases on consecutive heartbeats, affording cancellation of phase shifts induced by periodic cardiac motion (1).

In addition to phase accumulation during the bipolar pulses due to cardiac gross motion, there may also be unrecognized intravoxel incoherent motion (IVIM) effects within the duration of the bipolar pulses. Such IVIM effects may be caused by cardiac events such as myocardial fasciculation and perfusion, which could add additional diffusion signal to that of the myocardial intrinsic diffusion, and so will thereby increasing the apparent diffusion coefficient (ADC) of the myocardium. Examining these possible IVIM effects is crucial for evaluating the accuracy and motion sensitivity of the bipolar method, so a comparison between ADC measurement at cardiac moving phases (with possible IVIM effects) vs. cardiac standstill (excluding possible motion effects) is necessary. In the present study, little or no differences in ADC measurements were found between the moving and standstill phases. This directly demonstrates the insignificance of possible residual IVIM effects on diffusion, and thus validates the accuracy and motion-insensitivity of the current method.

The bipolar method described in this work affords the opportunity to examine the accuracy of the previously developed unipolar method, which addressed the cardiac motion problem by eliminating effects from the cardiac gross motion and the myocardial strain at significant costs of increased experimental complexity and reduced generality. This unipolar approach was shown to be effective. However, because of the complexities and limitations of the method, it is difficult to fully validate it by comparing diffusion measurement at moving phases vs. the standstill phase. Thus, the unipolar method is open to question in that it may be influenced by unrecognized forms or effects of cardiac motion. The bipolar method, which is shown to be free of motion effects, offers the opportunity to examine the accuracy of the unipolar method. By comparing the diffusion measurement results by the two methods, we seek to address the confounding question concerning the unipolar method.

Recent observation of random spontaneous contractile movement in cardiocytes raises the question of whether some fraction of the diffusion contrast in the present study may in fact have been produced by physiological movements (R. Balaban, personal communication). Such effects may be difficult to exclude. As such motions may occur throughout the cardiac cycle, they are not excluded by the present findings of constant diffusion over the cardiac cycle. Neither are they excluded by the finding that diffusion tensor fields match the known fiber architecture, as
they too may correlate with this architecture. However, evidence that spontaneous cellular fasciculation makes a minimal contribution to the present measurements is strongly supported by the equality of myocardial diffusion measured with the uni- and bipolar pulse sequences. While the uni- and bipolar experiments were constructed to have equal sensitivity to random diffusion, cellular fasciculation contains coherent components over the relevant time scales. These two experiments have markedly different sensitivities to such motion. According to a classic theory of generalized motion sensitivity, NMR signal attenuation may be predicted from the spectral overlap between the power spectrum of the autocorrelations of spin velocities with the power spectrum of the motion-encoding gradient waveform (14–17). If we assume that most of the power of the fasculatory motion is with a frequency band of 5–500 Hz, then the spectral amplitude of the bipolar experiment within this range is five to 60 times higher than that of the unipolar experiment because the bipolar gradient pulses are more intense and more numerous. It follows that such fasciculation should produce greater attenuation in the bipolar than in the unipolar experiments. Since we find that these data agree in absolute terms, we conclude that such effects are negligible in the present uni- and bipolar measurements. Experiments to map the spectral content of myocyte fasciculation can be contemplated may be helpful in this regard, perhaps with sinusoidal gradients for high spectral sensitivity and specificity (18).

Validation

The present studies in phantoms show that diffusion MRI with the bipolar method is independent of periodic motion and strain. The present in vivo studies show that the bipolar method measures no significant change in absolute diffusion from myocardial peak motion to myocardial standstill. This directly demonstrates that bipolar diffusion MRI is independent of myocardial motion per se.

The present measurements do show evidence of small but statistically significant differences in myocardial diffusion eigenvalues over the entire interval of contraction from end-diastole to end-systole. These differences may reflect changes in tissue architecture during contraction. The time samples in Fig. 6 are cardiac phases that include the full range of contraction rates from zero up to peak systolic motion. Accordingly, these data indicate that in the bipolar method the effect on diffusion contrast of any form of motion that varies with cardiac phase is unlikely to exceed the observed dynamic range of diffusion eigenvalues of 5–10%. To the extent that the curves shown in Fig. 6 do not have the forms expected for these effects, it seems more likely that the observed changes in diffusion are reflections of changes in myocardial architecture during contraction. Detailed temporal analysis cannot be undertaken with the present data, as diffusion changes on a 50–100-ms time scale do not achieve statistical significance. Elucidation of the cause of change in the observed myocardial diffusion will require further experimental studies, with improved sensitivity.

We also compared the bipolar method with the unipolar sweet spot method, and found that they showed agreement in measurements of myocardial diffusion. The agreement between the two methods provides cross-validation of both methods. First, it demonstrates that the sweet spot method is accurate and insensitive to cardiac motion effects. Second, it validates the accuracy of the bipolar method for in vivo studies, since the sweet spot method is a validated method for measuring in vivo myocardial architecture. Third, it demonstrates that the confounding cellular fasciculation effect is not the primary component of current diffusion measurements, i.e., current methods primarily and accurately measure the myocardial water diffusion.

The above results demonstrate that cardiac motion effects in cardiac diffusion MRI arise mostly from the recognized effects of myocardial gross motion and myocardial strain; other, unknown motion effects, if they exist, play little or no part. They also show that the in vivo cardiac diffusion MRI approaches developed to date—the unipolar sweet spot method and the bipolar method—are both accurate methods for measuring myocardial diffusion in beating hearts. However, compared with the unipolar method, the bipolar method offers clear advantages. Diffusion encoding in a single phase, and the strain-independent feature of the bipolar method eliminate the complexity and potential ambiguity of the unipolar method, and enable convenient and accurate imaging of myocardial diffusion in both normal and diseased hearts at any point in the cardiac cycle, as if the heart were arrested at that point. Thus, the bipolar method is a good standard for MRI diffusion measurements in beating hearts. With the bipolar method, multiple studies (which previously were difficult to perform using the unipolar method) can be conducted, such as fast and reliable imaging of the myocardial structure and its dynamics without contamination by cardiac motion and strain.

Strain Effect Within the Bipolar Pulses

In the present study the bipolar method was shown to be accurate and insensitive to the cardiac motion. However, to successfully apply this method there is one more experimental point that should be noted: the strain effect within the bipolar pulses. As previously described, the bipolar pulse limits the diffusion encoding to within the pulse duration. The two gradient lobes in the bipolar pulse are identical but opposite in sign, which in the ideal case results in a zero spatial modulation after the pulse, and thus produces no diffusion sensitivity in the intervening period between the two diffusion encoding pulses. However, in practice, due to myocardial strain (which stretches the spatial modulation within the pulse duration), the spatial modulation will not be exactly zero after the bipolar pulse. There will be some residual spatial modulation which will have diffusion sensitivity over the cardiac cycle. However, with a <30-ms duration of the bipolar pulse, this residual spatial modulation is negligibly small. Specifically, the residual spatial modulation \( k_{\text{residual}} \) produced by the bipolar pulse approximately equals the spatial modulation \( k_B \) produced by the encoding gradient times the strain occurring in the duration \( \delta_B \) of the de-encoding gradient, i.e., \( k_{\text{residual}} \approx k_B \delta_B S \), where \( S \) is the strain rate of the myocardium at the time of diffusion encoding. The
b-value $b_{\text{residue}}$ produced by $k_{\text{residue}}$ over one cardiac cycle $\Delta$ is approximately $b_{\text{residue}} \approx |k_{\text{residue}}|^2 \Delta = (|k_B| \delta_B S)^2 \Delta$. It follows that over one cardiac cycle, the ratio of $b_{\text{residue}}$ to the $b$-value produced by the bipolar pulses $B$ is:

$$b_{\text{residue}}/b_B \approx (|k_B| \delta_B S)^2 \Delta/(4/3 |k_B|^2 \delta_B) = 3/4 S^2 \delta_B \Delta. \quad [10]$$

In the present cases, $\delta_B \approx 13$ ms, $\Delta \approx 1$ s, and peak strain rate $S_{\text{peak}} \approx 1$ s$^{-1}$, which indicates that $b_{\text{residue}}/b_B \approx 1\%$, which falls below the present sensitivity. Thus, the bipolar pulses effectively encode the diffusion at a single cardiac phase as if the heart were frozen at that point. It is noted that this strain effect becomes significant at very much increased strain rates $S$ or measurement times $\Delta$, but could be ameliorated by reducing $\delta_B$.

It is also noted that in practical experiments, other factors such as noise, imperfect pulse triggering, nonlinear effect of the strain, etc., may also affect the diffusion measurement. Thus, the application of the bipolar method may not be as perfect as it is in theory. Nonetheless, the current experiments show that the bipolar method is capable of reducing the strain effect by at least 10-fold. With improved experimental management, it may be possible to increase the efficacy of the bipolar method in future studies.

Dynamics of Myocardial Fibers and Sheets

Using the bipolar method, we examined the myocardial sheet and fiber dynamics during systole in a normal human heart. The results showed that the myocardial sheets became more radially oriented, and the fibers became more longitudinally oriented, in agreement with previous results on canine hearts.

The motion- and strain-independent feature of the bipolar method makes it possible to study the myocardial sheet dynamics noninvasively in the cardiac cycle. The myocardial sheet is a recently observed laminar organization of the myocardium (19–21), the function of which is still a matter of active study. Study of the myocardial sheet in the past was mostly based on histology (12,22). Cardiac diffusion MRI offers the possibility of studying the sheet structure noninvasively (6,7). In beating hearts, it is difficult to study sheet dynamics using the unipolar method because of the complexities of the strain effect, which disrupts diffusion tensor measurements at points other than the sweet spot. The bipolar method, on the other hand, is strain-independent and can measure the sheet structure accurately at any point in the cardiac cycle. Our results on sheet dynamics in a normal subject using the bipolar method show that the sheets become more radially oriented during systole. The changes of the sheet angle during systole indicate that the sheet shear contributes to radial thickening, which is in agreement with the results obtained in canine hearts by LeGrice et al. (12), who found that the myocardial sheet shear can account for a substantial portion of systolic wall thickening. Since sheet shear is considered to be cellular rearrangement of the myocardium, our results on sheet dynamics show the existence of cellular rearrangement in the living human heart. The present observation that the sheets in the septum and the anterior freewall in parallel is also in agreement with the results obtained in canine hearts by LeGrice et al. (12), who found that the longitudinal-radial shear of the sheets in the septum and the anterior freewall are opposite in sign.

In the past, studies of fiber dynamics were typically based on histology (13) or used radio-opaque markers (23) within limited regions of the heart. The bipolar method offers the possibility of studying fiber dynamics directly and noninvasively, with the capability to examine any region of the heart. Our results on normal human subjects using the bipolar method show that the myocardial fibers of the left midventricle become more longitudinally oriented from early-systole to end-systole, which may indicate the torsion motion of the heart during contraction. This result is in agreement with that obtained in canine hearts by Streeter et al. (13), who found that the myofibers of the LV become more longitudinally oriented from end-diastole to end systole. In Streeter et al. ’s method, different canine hearts arrested at end-diastole and end-systole are used to observe the fiber dynamics, which is invasive and also requires careful and labor-intensive sample preparations. Using the present bipolar method, one can study the same heart at multiple points in the cardiac cycle noninvasively and efficiently, which offers clear advantages in examining the fiber dynamics.

It is noted that the current experiment used a large spatial resolution ($4 \times 4 \times 12$ mm) to achieve a sufficient signal-to-noise ratio (SNR). Although the results show that the current spatial resolution is effective in imaging the myocardial fiber and sheet architecture, further study will be required to assess the suitability of this resolution for clinical application.

Limitations of the Bipolar Method

The bipolar method is currently limited by the maximum gradient intensity routinely available for clinical MRI machines. The 40 mT m$^{-1}$ gradient we used is the maximum available at this time, which determines the utility threshold for application to human subjects. At this gradient intensity, the required diffusion-encoding time for the desired b-value is long, which lengthens the TE and reduces the SNR. As a result, the current bipolar method has limitations in spatial resolution and also in imaging time. On the other hand, the motion- and strain-independent feature of this method enables acquisition of cardiac diffusion MRI with interleaved multislices across the cardiac cycle, which could compensate for the currently low SNR. With increased gradient intensity, studies using the bipolar method can be performed in human subjects with higher resolution and efficiency.

CONCLUSIONS

We have presented a new cardiac diffusion MRI method which encodes diffusion in a single cardiac phase, and demonstrated that the new method is accurate and insensitive to cardiac motion and strain. We also compared the new method with previous diffusion MRI methodology valid in the normal heart, and demonstrated that both methods are accurate for in vivo studies. We mapped the systolic dynamics of myocardial sheets and fibers in nor-
mal humans, and found that myocardial sheets tilt toward the radial, and fibers tilt toward the longitudinal during contraction, as previously found invasively in canines. These results demonstrate that the present method has the capacity to measure myocardial diffusion accurately at any point in the cardiac cycle, as if the heart were immobilized at this point, and thus offers the capacity to map myocardial fiber structure and its dynamics with little or no contamination by cardiac motion.

REFERENCES