MR tagging demonstrates quantitative differences in regional ventricular wall motion in mice, rats, and men

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Rodents, especially rats and genetically manipulated mice, have played an important role in the exploration of molecular causes of human cardiovascular diseases (7). Many of these models have defects at the cellular level that lead to abnormalities in regional as well as global myocardial function. The popularity of these models raises the question of the similarities in the contractile behavior of the left ventricle (LV) between rodents and humans. Although it is generally assumed that similarities of global functional indexes are sufficient for clinical correlation, potential subtle differences in regional wall motion may not be appreciated with simple measures of global functions, such as ejection fraction or wall thickening. Such information is important in understanding the pathogenesis of various cardiac diseases.

At the microscopic level, the mammalian LV is composed of obliquely running sheets of fibers that course in a helical spiral from apex to base. Armour and Randall (2) reported a similar arrangement of fiber orientations in nine mammalian species ranging in size from ground squirrel to elephant. A similar structure was also identified in humans from in vivo MRI studies (23). Our own observations using diffusion tensor magnetic resonance (MR) imaging also revealed similar myocardiarchitecture for both rat (6) and mouse (unpublished observations). These similarities in myofiber architecture suggest that the fundamental patterns of wall motion such as torsion, longitudinal and circumferential shortening, and wall thickening may be similar among mammalian species.

However, there are also considerable differences between humans and rodents at both the microscopic and macroscopic levels. Besides the dramatic differences in scale and hemodynamics, sarcomeric protein composition also differs significantly. In human ventricles, β-myosin heavy chain (β-MHC) is the predominant isoform, comprising >90% of the total myofibrillar myosin. In contrast, α-MHC isoform predominates and comprises >95% of the total myofibrillar myosin protein in the ventricles of mice and rats (9, 27). The relative distribution of the α-MHC and β-MHC isoforms in the myocardium may lead to different phenotypic expression of cardiac diseases, as was demonstrated in two recent studies of transgenic rabbit models of altered sarcomeric proteins (17, 25). It is possible that such different phenotypic expression may arise from the differences in ventricular wall mechanics due to the differences in the distribution of sarcomeric protein isoforms.

Indeed, the comparability of ventricular function between humans and mice has been controversial. It was reported previously that left ventricular torsion, a component of normal systolic function, was equal in mice and humans, suggesting a much smaller twist angle in mice than in humans (2° vs. 10°) (16). However, Zhou et al. (29) reported more recently a twist angle around 8° in mice, which was similar to the twist angle observed in humans (around 10°), indicating much larger torsion in mice. Mathematical modeling suggests that torsion may serve to equalize the transmural distribution of myocardial fiber stress (3, 4). Therefore, accurate quantification of torsion, as well as other regional wall motion parameters, is important...
in elucidating the difference in disease expression between humans and rodent models.

To fully understand the basic wall motion mechanics in mammalian hearts in vivo, we quantified regional and global indexes of ventricular wall motion in mice, rats, and men. MR tagging has been shown to yield accurate and reliable quantification of the regional cardiac function in humans (1, 12, 20, 26). With the advance in MR imaging technology and small animal monitoring, it is feasible now to assess the regional wall motion in small animals (8, 11, 16, 19, 29). Accordingly, we used MR tagging to quantify regional and global myocardial wall motion, as well as other morphological features that may alter the motion patterns.

MATERIALS AND METHODS

MR imaging of mice and rats. C57BL/6 mice (male, 1.8 ± 0.3 mo; n = 7) and Fischer 344 rats (male, 23.5 ± 1.2 mo; n = 6) underwent MR imaging on a 4.7-T Varian INOVA system (Varian Associates, Palo Alto, CA) equipped with a gradient insert (60 G/cm, 10 cm inner diameter). Surface coils of 2.5 and 5 cm were fabricated for the imaging of mice and rats, respectively. Animals were anesthetized with 0.7–1% isoflurane by a nose cone and placed into the coil in prone position. Electrodes were attached to front paws and right leg for ECG gating and monitoring of vital signs. The animals were kept warm by blowing hot air into the magnet using a blow dryer. The heat flow and the anesthesia level were manually adjusted to maintain the heart rate close to that under conscious conditions. The animal protocol was approved by the Animal Studies Committee of the Washington University Medical Center.

A horizontal long-axis view was acquired perpendicular to the interventricular septum. Three short-axis (SA) slices, parallel to the tricuspid and mitral valve plane, were imaged at basal, midventricular, and apical levels. The midventricular slice was chosen at 50% of the distance between the atrioventricular valve plane and the apex. Basal and apical slices were chosen 2 and 3 mm above and below the midventricular slice in mice and rats, respectively.

Myocardial tagging was performed with two sets of SPAMM1331 sequences, with a total duration of 7 ms, executed sequentially after the detection of R wave to generate stripe tags in two orthogonal directions in one acquisition series. Tagged cine images were acquired with ECG-gated gradient-echo sequence using the following parameters: flip angle, 30°; echo time, 3 ms; data matrix, 256 × 256. The field of view was 4 cm × 4 cm for mice and 6.5 cm × 6.5 cm for rats. The slice thickness was 1 mm for mice and 1.5 mm for rats. Repetition time was adjusted according to the R-R interval of the heart. Fifteen frames were acquired during one cardiac cycle, yielding a temporal resolution of 8 ms in mice and 14 ms in rats. The temporal resolution enabled the coverage of systole with seven or eight frames in rats and six or seven frames in mice. The tag resolution was ≈0.6 mm for mice and ≈0.9 mm for rats, allowing three or four tag lines to be placed across the ventricular wall of rats (Fig. 1, A and D) and two or three tag lines for mice (Fig. 1, B and E). The tagged images were zero filled into a 512 × 512 data matrix.

Regular cine images that provided better contrast between myocardium and the blood were acquired with a 128 × 128 data matrix with

![Fig. 1. Representative tagged short-axis images from rat (A and D), mouse (B and E), and male patient (C and F) at end diastole (A–C) and end systole (D–F).](http://ajpheart.physiology.org/)

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parameters similar to the tagged images for the calculation of morphological parameters and ejection fraction. The cine images were also zero filled into a 512 × 512 data matrix, such that myocardial contours traced from cine images were directly used in the analysis of tagged images with minimal adjustments.

**MR imaging of men.** Healthy male volunteers (11.6 ± 2.7 years; n = 6) recruited from a pediatric clinic at Washington University Medical Center were scanned on a 1.5-T Intera whole body MR system (Philips Medical Systems, Best, The Netherlands). Written informed consent was obtained from each subject’s parent or legal guardian before the study, which was approved by the Institutional Review Board of the Washington University Medical Center. To ensure that data were comparable between subjects, the same imaging protocol used for animals was followed with acquisition parameters scaled for human hearts. Cine images of contiguous SA planes from the mitral valve plane to the apex were obtained with an ECG-gated gradient-echo sequence. Normal cardiac structure and wall motion of the myocardium in homogeneous strain analysis. The cine images were confirmed with the standard cine images before tagging.

The tagging mesh was traced interactively by use of coupled cubic spline snakes (19). These snakes were constructed by having the horizontal and vertical lines share the control points such that horizontal and vertical lines would both deform to fit the corresponding tags when a control point shared by these two lines was moved (Fig. 2C). The intersecting tag points were tracked semi-automatically by harmonic phase technique (21). Once tag tracing was finished, the myocardium was divided into nonoverlapping triangular tissue elements, using sets of adjacent tag points as the vertices (Fig. 2D). Regional myocardial wall motion across the SA plane of the ventricle was visualized by tracking the displacement of the centroid of each triangle (Fig. 2E).

Myocardial twist and radial shortening were computed relative to the center of ventricular cavity with the use of the method outlined in Fogel et al. (12). As shown in Fig. 2F, radial shortening, a measure of the displacement of the centroid of each triangle, was calculated as |P1|−|Pn|, where P1 and Pn are vectors from the centroid of the cavity to the centroid of a triangle at phase 1 and n, respectively. Positive shortening values represented net inward wall motion of each trian-

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**Fig. 2.** A: short-axis image of a rat heart overlaid with endocardial and epicardial contours. Red dots are the control points used in B-spline contour tracing. LV, left ventricle. B: horizontal long-axis view of a rat heart. C: short-axis tagged image overlaid with semiautomatically tracked tagging mesh. D: triangulation of the myocardium in homogeneous strain analysis. E: visualization of myocardial wall motion from end diastole to end systole by following the motion of the centroid of each triangular element. F: quantification of myocardial wall motion by quantifying the displacement of the triangular center and the deformation of the triangle. P1 and Pn, vectors from the centroid of the cavity to the centroid of a triangle at phase 1 and n, respectively; θ, twist angle.
Table 1. Morphological characteristics of LV and ejection fraction

<table>
<thead>
<tr>
<th></th>
<th>Diameter, mm</th>
<th>Length, mm</th>
<th>Wall Thickness, mm</th>
<th>Wall Thickness/Radius</th>
<th>Radius/Length</th>
<th>Ejection Fraction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>58.1±6.0</td>
<td>82.4±7.0</td>
<td>6.35±1.07</td>
<td>0.22±0.03</td>
<td>0.35±0.02</td>
<td>59.1±3.6</td>
</tr>
<tr>
<td>Rats</td>
<td>11.0±0.3</td>
<td>12.8±1.0</td>
<td>1.83±0.09</td>
<td>0.33±0.01</td>
<td>0.44±0.03</td>
<td>67.3±6.6</td>
</tr>
<tr>
<td>Mice</td>
<td>5.1±0.4</td>
<td>7.7±0.5</td>
<td>0.90±0.06</td>
<td>0.35±0.04</td>
<td>0.35±0.01</td>
<td>61.3±8.1</td>
</tr>
</tbody>
</table>

Values are means ± SD. LV, left ventricle. *P < 0.001 compared with rats and mice; †P < 0.001 compared with men and mice.

gle’s centroid toward the ventricular cavity relative to the end-diastolic distance. To account for the differences in heart size among different species, radial shortening was normalized by the LV radius to yield normalized radial shortening (5). Twist angle was defined as the rotation of the centroid of the triangles from end diastole to end systole. Positive twist represented clockwise rotation viewed from base. Net twist angle was defined as the difference between the ventricular twist at apical and basal slices. Torsion was calculated as the net twist angle normalized by the slice separation. Lagrangian strain tensor was computed in each triangle by use of homogeneous strain analysis. This approach assumes that deformations within each triangle are locally homogeneous. Lagrangian strain tensor was further projected onto the circumferential direction to yield circumferential strain.

Statistical analysis. We used unpaired Student’s t-tests for comparisons between two groups. Differences among the three species (men, rats, and mice) were analyzed by ANOVA. All measurements are presented as means ± SD. P values <0.05 were considered statistically significant.

RESULTS

Physiological characteristics and LV morphology. Average body weight was 41.2 ± 10.7 kg for men, 429 ± 40.0 g for rats, and 26 ± 1.0 g for mice. The body surface area of the male volunteers was in the normal range (1.28 ± 0.21 m²). Smaller species showed increased heart rate: 78 ± 8 beats/min for men, 278 ± 21 beats/min for rats, and 436 ± 63 beats/min for mice. Morphological data and ejection fraction are presented in Table 1. Besides the obvious differences in heart sizes, wall thickness-to-LV radius ratio was significantly smaller in men than in rats and mice (P < 0.001). However, the LV radius-to-length ratio was the same in men and mice, whereas it was significantly larger in rats (P < 0.001), suggesting that rats have a more spherical LV. Despite large variations in body weights and heart sizes, the ejection fraction was similar in mice, rats, and men (P = not significant).

Ventricular twist and torsion. Figure 3A illustrates the twist (rotation angle) patterns in mice, rats, and men at apical, midventricular, and basal levels. The LV twisted clockwise at apex in all three species: 8.7 ± 3.2° in mice, 9.0 ± 2.3° in rats, and 9.7 ± 2.9° in men (P = not significant). Twist was counterclockwise at basal level with no significant differences among mice (−4.1 ± 1.8°), rats (−5.6 ± 1.9°), and men (−3.5 ± 1.0°). As a result, net ventricular twist was also similar among mice, rats, and men (12.8 ± 2.0°, 14.5 ± 0.9°, and 13.2 ± 2.2°, respectively, P = not significant) as shown in Fig. 3B. However, because of the considerable differences in LV length, torsion (net twist per unit length) was significantly greater in mice and rats than in men (Fig. 3C): 31.5 ± 4.7°/cm in mice, 23.1 ± 2.7°/cm in rats, and 3.6 ± 0.7°/cm in men (P < 0.001). To account for the differences in ventricular size, radius × torsion was also calculated. It was the largest in rats and the smallest in mice (rats: 12.7 ± 1.8°, men: 10.2 ± 1.2°, mice: 8.2 ± 1.3°; P < 0.05 for each pair).

Circumferential strain and normalized radial shortening. The strain pattern was similar in men, rats, and mice. However, the magnitude of both circumferential strain and normalized radial shortening differed significantly. Circumferential strain...
was the greatest in men at all three levels (Fig. 4A and Table 2). Normalized radial shortening was also greater in men than in rats and mice (Fig. 4B and Table 2). In addition, the longitudinal shortening in men (0.24 ± 0.03) was significantly greater than that in mice (0.14 ± 0.01; P < 0.001) and rats (0.19 ± 0.01; P < 0.001).

**DISCUSSION**

With the growing popularity of rodent models in cardiovascular research, comprehensive analysis and comparison of the contractile function between rodents and humans are important to the understanding of the pathogenesis of human cardiac diseases from laboratory observations of animal models of these diseases. Compared with conventional imaging modalities that measure global functional indexes, MR tagging has the advantage of comprehensive evaluation of regional myocardial function, as well as the delineation of complex wall-motion mechanics. In the present study, ventricular twist and torsion, as well as circumferential strain and normalized radial shortening, were measured with the use of MR tagging in mice, rats, and men. Our data demonstrated that ventricular twist was conserved across these species, whereas torsion, measured as twist per unit length, was smaller in the larger species. However, circumferential strain and normalized radial shortening were larger in humans. Although other parameters, such as circumferential-longitudinal (CL) shear strain, need to be evaluated, these quantitative differences in myocardial wall motion may lead to different phenotypic expression in response to altered pathophysiological conditions.

Our observations of similar twist angles but large torsion in small species are consistent to those reported by Zhou et al. (29). More recently, Gilson et al. (15) quantified twist and torsion in mice with a novel technique called displacement-encoded imaging using stimulated echoes. They also estimated a net twist value of ~11° for the entire mouse heart (15). However, Henson et al. (16) reported similar torsion between mice and humans in an earlier study. This discrepancy may stem from the specific methods used to measure ventricular twist. First, end-systolic twist angle was measured in our study, whereas that reported by Henson et al. was the twist angle at 80% of the systole. Also, a higher tagging resolution of ~0.6 mm was achieved in mice in our study compared with the 1.2-mm tagging resolution in the study reported by Henson et al. More importantly, although Henson et al. used a DANTE train with 32 pulses for their tagging studies of mice, the present study used a SPAMM1331 tagging sequence that was similar to that used by Zhou et al. (29), resulting in significantly shorter time for the implementation of the tagging sequence. Because the duration of the QRS complex is very short for mice and rats (<20 ms), longer tagging time may delay the subsequent image acquisition such that the first frame is acquired when the heart is already in the contracting state. Accordingly, the acquired reference frame for strain and twist calculation may not be from end diastole.

Although the net twist in mice observed in the present study was similar to that reported in previous studies (15, 29), the calculated torsion was larger because of the differences in torsion calculation. Although both Zhou et al. and Gilson et al. used net twist normalized by LV length as a measure of torsion, we calculated torsion as net twist normalized by the distance between the basal and apical slices. In addition, the distance between apical and basal slices in the study of Gilson et al. was only 3 mm apart, whereas it was 4 mm apart in the present study. Despite these differences, all three studies demonstrated that torsion of the mouse heart is much larger than the torsion in the human heart.

The underlying mechanisms for the observed differences in myocardial wall motion between humans and small animals remain to be elucidated. The ratio of wall thickness to radius was significantly smaller in humans. Because ventricular torsion is due to the contraction of obliquely oriented fibers in competing orientations at the endocardium and epicardium, the

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**Table 2. Myocardial strains**

<table>
<thead>
<tr>
<th></th>
<th>Apex</th>
<th>Midventricle</th>
<th>Base</th>
<th>Apex</th>
<th>Midventricle</th>
<th>Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>−0.22±0.03</td>
<td>−0.21±0.02</td>
<td>−0.20±0.01</td>
<td>0.18±0.05</td>
<td>0.23±0.02</td>
<td>0.21±0.02</td>
</tr>
<tr>
<td>Rats</td>
<td>−0.21±0.01</td>
<td>−0.19±0.01†</td>
<td>−0.16±0.02†</td>
<td>0.16±0.04</td>
<td>0.19±0.02†</td>
<td>0.14±0.03†</td>
</tr>
<tr>
<td>Mice</td>
<td>−0.18±0.02†</td>
<td>−0.15±0.02†</td>
<td>−0.13±0.01†</td>
<td>0.13±0.03*</td>
<td>0.14±0.03†</td>
<td>0.10±0.02‡</td>
</tr>
</tbody>
</table>

Values are means ± SD. *P < 0.05 compared with men; †P < 0.001 compared with men; ‡P < 0.001 compared with rats.
epicardium has a mechanical advantage because of a larger moment arm. Therefore, changes in the ratio of wall thickness to radius alone may alter ventricular torsion (28). The smaller wall thickness-to-radius ratio in humans may lead to a relatively smaller mechanical advantage of the epicardial fibers in torsion. On the other hand, torsion is also considered a major mechanism for the ejection of blood. Despite the differences in their body weights and heart sizes, the ejection fraction was similar in mice, rats, and men. The observed enhancement in normal strains in humans seems to have compensated for the reduced torsion in larger species.

Twist per unit length was used as a measure of torsion in the present study to compare our data with previous studies. Such measure is not scale invariant. Because torsion reflects the underlying shearing motion of the myocardium, the CL shear strain can serve as a scale-invariant measure of ventricular torsion. However, such quantification is only available through three-dimensional analysis. Alternatively, to account for the difference in ventricular size, we also evaluated radius × torsion as a unitless measure of torsion; it was largest in rats. Further investigation through mathematical modeling is needed to fully understand the quantitative relationship between torsion and other modes of myocardial deformation. Also, it is not known whether the observed quantitative differences in myocardial deformation may result in different stress distribution. Such difference may play a role in the observed differences in disease progression of different animal models (18, 24).

As in most animal studies, rats and mice were anesthetized during the entire course of MRI scan. The heart rate was lower than those reported in conscious rats and mice, which may lead to depressed contractile behavior of the heart. However, the ejection fraction was similar in mice, rats, and humans in the present study. In addition, our data suggest that not every parameter of myocardial wall motion, e.g., twist and torsion, was reduced in anesthetized mice and rats. Hence, it is unlikely that the observed decrease in circumferential strain and normalized radial shortening in rats and mice is attributable solely to the effects of anesthesia. Also, rats in this study were of an older age group, whereas humans and mice were at about the same maturation stage. Although ventricular morphology and function may change slightly with age, wall thickness-to-radius ratio was similar between mice and rats. In a recent study, Oxenham et al. (22) reported unaltered myocardial strains but slightly increased apical rotation with aging. Net twist in rats was slightly higher than that in mice and humans in the present study (Fig. 3B). However, no statistical significance was detected.

One limitation of the present study is that only two-dimensional tagging analysis was performed. Hence, errors due to the through-plane motion cannot be corrected. In addition, the CL shear, the scale-invariant measure of ventricular torsion, cannot be quantified from two-dimensional tagging. Instead, we used twist per unit length as a measure of torsion for the purpose of interlaboratory comparison. Because torsion is essentially a shear motion in the CL direction, further investigation is needed to examine whether the scale-invariant CL shear is conserved across species. Also, radial strain was not presented in the present study. Compared with circumferential strain, radial strain calculated from strain tensor is more prone to noise because of the limited number of triangular elements in the radial directions. As a result, many investigators focused on circumferential strain only (10, 11, 14). Alternatively, Fogel et al. (12, 13) used radial shortening, i.e., myocardial motion in the radial direction, as a measure of radial wall motion. In this study, we used the scale invariant radial shortening, i.e., radial shortening normalized by LV radius, for interspecies comparison.

In conclusion, we found that ventricular twist, but not torsion, was conserved in mice, rats, and humans. Accordingly, ventricular twist may provide the most direct correlation of contractile parameters in different species. The smaller torsion in larger species may have been compensated by the greater normal strains to generate similar ejection fraction. Although the causes and implications of these differences in contractile behavior remain to be elucidated, the preservation of twist appears fundamental to cardiac function and should be considered in studies that extrapolate observations from rodent to human.

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