Published in final edited form as:

J Magn Reson Imaging. 2010 September ; 32(3): 608–614. doi:10.1002/jmri.22256.

Quantification of Myocardial Strain at Early Systole in Mouse Heart: Restoration of Undeformed Tagging Grid with Single-Point HARP

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Abstract

Purpose—To develop accurate strain and torsion quantification method for the assessment of myocardial contraction in mice by MRI tagging.

Materials and Methods—Ventricular wall motion at baseline and during β -adrenergic stimulation was assessed in mice using MRI tagging. Myocardial strain and torsion were quantified using finite element analysis method. A harmonic phase (HARP) based method was developed for the restoration of undeformed taglines for more accurate calculation of myocardial wall strain and torsion.

Results—Myocardial deformation was observed at early systole (< 20 ms after QRS) both at baseline and during β -adrenergic stimulation. The HARP-based method allowed robust restoration of undeformed taglines that can be used as the reference in finite element analysis of the tagged images. Without such correction for myocardial deformation in the reference image, inaccuracy in strain quantification underestimated significant strain development at early systole in dobutamine-stimulated hearts.

Conclusion—The HARP-based method developed in the current study enabled automated restoration of undeformed taglines in mouse hearts, leading to more accurate calculation of myocardial wall strain and torsion during dobutamine stimulation.

Keywords

Harmonic Phase (HARP); myocardial contractility; β -adrenergic stimulation; MRI tagging

MR tagging is a valuable technique in evaluating regional contractile performance of the heart (1–3). The application of MR tagging to genetically manipulated mouse models of cardiac diseases allows the opportunity to elucidate the molecular mechanisms of abnormal cardiac function (4–7). Current tagging analysis frequently employs finite element method for quantification of regional myocardial wall strains (5–9). These methods use the first tagged image, which is acquired immediately after the implementation of the tagging

sequence, as the reference frame, with the underlying assumption that taglines in this image are undeformed. Such assumption requires that the first tagged image be acquired within the QRS complex before significant myocardial contraction occurs. For humans and large animals, the duration of QRS complex (about 100 ms) is sufficiently long to ensure that the first tagged image is acquired within the QRS complex during ventricular depolarization. However, for a mouse heart, the QRS complex is typically less than 20 ms in duration (10), followed by a rapid phase of contraction due to the fast heart rate. As a result, the first tagged image is frequently acquired at early systole with significant tagline deformation. This deformation can be even more pronounced in hearts under β -adrenergic stimulation as a consequence of enhanced ventricular contractility (11–13). Therefore, using the first frame as the reference frame can lead to significant underestimation of myocardial strains in mouse heart.

Recently, methods based on harmonic phase (HARP) analysis have been proposed for direct calculation of myocardial strain maps, as well as for semi-automated tracking of the deformed taglines (14–17). However, direct strain quantification from HARP images requires phase unwrapping and calculating the spatial derivatives of the unwrapped HARP images, which may amplify imaging noise due to its nature of high-pass filtering. Further, ventricular torsion, a sensitive index of ventricular dysfunction, cannot be directly quantified using this method. Hence, finite element analysis in combination with semi-automated tagline tracking remains a viable method in the analysis of tagged MR images.

In the current study, we developed a HARP-based method to restore the undeformed taglines for strain and torsion quantification employing finite element analysis. Using this method, myocardial contraction at baseline and during β -adrenergic stimulation was analyzed. Our results show that significant deformation occurred at early systole, characterized by nonzero strain and torsion values. Strain calculation without correcting for early myocardial deformation in the reference frame showed significant underestimation of ventricular contraction. Such inaccuracy diminished the differences in contractile performance between baseline and β -adrenergic stimulation.

MATERIALS AND METHODS

Animal Preparation

Wildtype C57BL/6 mice (n=11, 37–43 weeks old) were scanned on a Bruker 7T scanner (Bruker BioSpin, Billerica, MA) with a volume RF coil. Mice were anesthetized with 1.5% isoflurane by a nose cone and placed into the coil in prone position. A 26G Abbocath®-T catheter (Hospira, Donegal Town, Ireland) was inserted into the tail vein and connected to an infusion pump (Harvard Clinical Technology, North Natick, MA) for dobutamine infusion. Electrodes were attached to one front and one rear leg for ECG gating and monitoring of vital signs. Rectal thermometer was used to monitor the body temperature. The ECG electrodes and the thermometer were connected to an MR-compatible system (SA Instruments, Stony Brook, NY) that generated TTL signals for triggering the MR scanner. Body temperature was maintained by blowing hot air into the magnet that was controlled by a feedback system. The desired body temperature was set at 34°C to reach a heart rate comparable to that reported in literature (4). The animal protocol was approved by the Institutional Animal Care and Use Committee in our institution.

MR Imaging

Short-axis imaging planes were prescribed as described previously (7,18). Tagged images of 3 short-axis slices at basal, midventricular, and apical levels were acquired with 1 mm slice thickness. The mid-ventricular slice was chosen at 50% of the distance between the

atrioventricular valve plane and the apex. The apical and basal slices were chosen at 1.5 mm above or below the mid-ventricle slice, respectively. The tagging sequence used a 1331 SPAMM sequence applied immediately after the ECG trigger, followed by a gradient-echo cine sequence. The duration of the tagging module was ~7 ms. Two sets of SA images with tags in orthogonal directions were acquired. For each acquisition, repetition time (TR) was adjusted according to the R-R interval of the heart such that 15 frames were acquired in a cardiac cycle. Variation in TR was 8–10 ms over the duration of the experiment. Other imaging parameters were: flip angle, 25°; TE, 2.2 or 2.5 ms; field of view (FOV), 4 cm×4 cm or 3.5cm×3.5cm; matrix size, 256×128; tagging resolution, 0.6 mm.

Following the acquisition of MR images at baseline, the mouse was continuously infused with 40 µg/kg/min dobutamine (Bedford Laboratories, Bedford, OH). The increase in heart rate took approximately 5 minutes to peak and stabilize. Tagged and cine images were then acquired at the same short-axis positions with the same imaging parameters as those at the baseline.

Regular cine images that provided better contrast between the myocardium and the blood were acquired before and during dobutamine stimulation at the same basal, midventricular, and apicals level prescribed for tagged image acquisition. These images were acquired with the same imaging parameters as the tagged images and with a 128×128 data matrix. Both the cine and the tagged images were 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.

Image Analysis

An in-house developed, MATLAB-based software was modified for image analysis (7,18–21). The method for restoration of undeformed taglines is based on the theory that the SPAMM modulation of an MR image takes the form of a sinusoidal dependence of the longitudinal magnetization (2,3). It produces an array of spectral peaks (harmonic peaks) in the Fourier domain (k-space, Fig. 1a). Therefore, a tagged image can be represented by a series of Fourier transformed harmonic peaks as (15)

$$I(\mathbf{p}) = \sum_{k=-K}^K c_k I_0(\mathbf{p}) e^{j\omega_k^T \mathbf{p}}$$

where $I_0(\mathbf{p})$ is the original image without SPAMM modulation, K is determined by the tagging sequence ($K=1$ and 2 for 11 SPAMM and 1331 SPAMM, respectively), c_k 's are coefficients determined by the tip angles of the SPAMM sequence, and ω_k 's are the frequency vector determined by the strength and duration of the tagging gradients. Using the following definition of the displacement field ($\mathbf{u}(\mathbf{x}, t)$) of a material point $\mathbf{p}$,

$$\mathbf{u}(\mathbf{x}, t) = \mathbf{x} - \mathbf{p}(\mathbf{x}, t)$$

each harmonic peak can, therefore, be expressed in expanded form as

$$I_k(\mathbf{x}, t) = c_k I_0(\mathbf{x}, t) e^{j\omega_k^T \mathbf{x}} e^{-j\omega_k^T \mathbf{u}(\mathbf{x}, t)} \quad [1]$$

The first exponential term in [1] represents a complex sinusoidal modulation with frequency ω_k , while the second exponential term represents additional phase modulation associated with the displacement of the material point. In the Fourier domain, the sinusoidal modulation will shift the center of the harmonic peak to ω_k . Due to the dominance of stationary tissues within the image field of view, this center of the harmonic peak will not be shifted by myocardial displacement (the second exponential term) associated with ventricular contraction. Hence, selecting a single point at the center of the first-order harmonic peaks will yield a sinusoidal function in the form of $e^{j\omega_k^T x}$ in the spatial domain. The undeformed taglines can thus be fully recovered by taking the π iso-contours of this function.

To reconstruct the undeformed taglines, a single point corresponding to the maximum of the first-order harmonic peak was extracted from the k -space data (Fig. 1a). To eliminate the digitization errors, the π iso-contours were calculated from the inverse Fourier transform of this single-point harmonic peak and its four neighbor points. The intersecting points of these π iso-contours in two orthogonal directions were used as the reference tag points for subsequent tag tracking and strain computation. The displacement of these tag points were tracked semi-automatically by HARP-based approach using a circular filter with a radius of 25 pixels for images with 3.5cm×3.5cm FOV and 30 pixels for images with 4cm×4cm FOV.

Following tag tracking, 2D Lagrangian strain tensor was calculated using homogeneous strain analysis method as described previously (7). Briefly, myocardium was divided into non-overlapping triangular tissue elements using sets of adjacent tag points as the vertices. Lagrangian strain tensor ($\mathbf{E}$) was computed for each triangle. $\mathbf{E}$ was also diagonalized to yield two principal strains corresponding to maximum stretching and maximum shortening, respectively. Circumferential (E_{cc}) and radial (E_{rr}) strains were then calculated from the projection of the two principal strains on the circumferential and radial directions. Average strain values of the whole short-axis slice were calculated. Myocardial twist was computed as the rotation angle around the center of LV cavity. Positive twist indicated clockwise twist viewed from apex. Net twist angle was defined as the difference between the ventricular twist at basal and apical slices. Torsion was calculated as the net twist angle normalized by the slice separation. Circumferential strain and torsion rates were calculated from the time course of the circumferential strain and ventricular torsion, respectively.

Statistical Analysis

Data are presented as mean $\pm$ standard deviation. Comparisons of ventricular contractility between baseline and dobutamine stimulated hearts were performed using unpaired Student t-test. Paired Student t-test was employed for comparisons of strains computed from the same image sets with or without correcting for early systolic deformation. $P < 0.05$ was considered statistically significant.

RESULTS

Animal Characteristics

Average body weight of the mice was 34.2 ± 3.78 g. The heart rate during MRI scanning was 419 ± 44 BPM and increased to 480 ± 31 BPM during dobutamine infusion ($P < 0.01$). At the midventricular level, LV diameter decreased from 5.68 ± 0.05 mm at end-diastole to 5.35 ± 0.20 mm at end-systole, while wall thickness increased from 0.99 ± 0.05 mm to 1.62 ± 0.10 mm at baseline. During dobutamine stimulation, LV diameter decreased from 5.54 ± 0.07 mm to 5.22 ± 0.29 mm, wall thickness increased from 1.04 ± 0.07 mm to 1.78 ± 0.24 mm. The ejection fraction increased from $65 \pm 6\%$ at baseline to $77 \pm 6\%$ during dobutamine infusion ($P < 0.01$).

Tag Tracking and Generation of Undeformed Tagging Grid

As shown in Fig. 1, π -isocontours calculated from the first-order harmonic peaks (Fig. 1a, yellow filter) overlapped with the deformed taglines in the myocardium (Fig. 1b, yellow lines). However, π -isocontours determined from single-point harmonic peaks (Fig. 1a, magenta filter) overlapped with the taglines in the stationary tissues. Deformation at early systole was visible by comparing the two tagging grids (Fig. 1b).

To examine the robustness of our method, we also extracted single-point harmonic peaks from all subsequent tagged images. The positions (ω_k) of these harmonic peaks in k-space were the same as those in the first frames, indicating unaltered frequency modulation. As shown in Fig. 1c, the restored taglines from a tagged image acquired at peak-systole were identical to those generated from the first tagged image.

Myocardial Deformation at Early Systole

Using tagging grids generated from single-point HARP images, myocardial strains and twist at early systole were calculated from the first tagged images (Fig. 2). Nearly all reference images showed deformed taglines, evidenced by the non-zero strains and twists. Compare to baseline, significant circumferential shortening (E_{cc}) occurred at early systole in dobutamine-stimulated hearts ($P < 0.05$ at apex and mid-ventricle), with all three slices exhibited negative mean E_{cc} values ranging from -0.012 to -0.016 . Compare to that at the baseline, the magnitude of E_{cc} was significantly increased in dobutamine-stimulated hearts at midventricle ($P < 0.01$) and apex ($P < 0.05$). Average E_{cc} of the first image was approximately 10% of the peak circumferential strain in mice subject to dobutamine stimulation.

Positive radial strain was present in early systole both at baseline and under dobutamine stimulation. Dobutamine-stimulated hearts showed a trend of increased radial strain. However, no statistical significance was detected. E_{rr} at baseline and during dobutamine stimulation were 0.019 ± 0.016 and 0.029 ± 0.027 at apex ($P = 0.40$), 0.021 ± 0.018 and 0.040 ± 0.022 at midventricle ($P = 0.11$), and 0.014 ± 0.008 and 0.030 ± 0.018 at base ($P = 0.06$), respectively.

The hearts also displayed variable twist at early systole, ranging from -1.91° to 0.57° at baseline, and -3.25° to 1.46° during dobutamine infusion. Mean twist angles at base, mid-ventricle and apex were similar at baseline ($-0.73 \pm 1.01^\circ$, $-0.61 \pm 0.87^\circ$, and $-0.59 \pm 0.67^\circ$, respectively). With dobutamine stimulation, twist angle showed progressive increase from apex to base ($-0.77 \pm 1.34^\circ$, $-0.32 \pm 1.19^\circ$, and $0.03 \pm 1.04^\circ$ at base, mid-ventricle and base, respectively). As a result, early ventricular torsion during dobutamine stimulation was slightly increased from $0.05 \pm 0.23^\circ/\text{mm}$ at baseline to $0.27 \pm 0.36^\circ/\text{mm}$ during dobutamine infusion ($P = 0.20$).

Ventricular Contraction in Response to β -Adrenergic Stimulation

The time courses of ventricular twist and torsion are shown in Fig. 3. In addition to increase in heart rate, dobutamine-stimulated hearts also exhibited significantly increased twist at apex (Fig. 3a), leading to enhanced ventricular torsion during systole (Fig. 3b). The peak torsion increased from $3.02 \pm 0.68^\circ/\text{mm}$ at baseline to $4.60 \pm 0.29^\circ/\text{mm}$ under dobutamine stimulation ($P < 0.0001$). Consistent with increased torsion in systole, there was also a significant increase in circumferential shortening (E_{cc}) at all three levels (Fig. 4). E_{cc} at peak systole showed significant difference at midventricle and base ($P < 0.05$).

Fig. 5 shows peak circumferential stain and torsion rates during systole and diastole. Dobutamine induced significant increase in torsion rate during both systole and diastole.

There was also a significant increase in peak circumferential strain rate at all three levels during systole. During diastole, there was a trend of increased circumferential strain rate with statistical significance at basal level ($P<0.05$).

Comparison to Strain Quantification without Correction for Reference Deformation

To evaluate errors in strain quantification without correcting for early tagline deformation, we also calculated circumferential and radial strains with direct reference to the first tagged image in a cine series and compared such calculation to results using the current method (Fig. 6). Without correction, the calculated E_{cc} at peak systole was 1% to 10% lower than those using the current method, especially during dobutamine stimulation ($p<0.05$ for all three levels). Peak E_{tr} also showed similar underestimation both at baseline and under dobutamine stimulation. Such underestimation diminished the contractile difference between baseline and dobutamine stimulation, as no statistical significance in peak E_{cc} was detected between the two groups if images were processed without correction.

Similarly, ventricular torsion calculated from deformed reference frame was also lower compared to the results from the current method. Using the current method, peak torsion changed from $3.02\pm0.68^\circ/\text{mm}$ at baseline to $4.60\pm0.29^\circ/\text{mm}$ during dobutamine stimulation ($P<0.001$). Without correction, ventricular torsion was $2.92\pm0.72^\circ/\text{mm}$ and $4.34\pm0.42^\circ/\text{mm}$ at baseline and during dobutamine stimulation, respectively ($P<0.001$).

DISCUSSION

HARP method was first proposed as a semi-automated approach to track deformed taglines (14). Such approach is based on the fact that tissue motion is directly encoded in the phase image of the off-center spectral peaks. The single-point HARP method developed in the current study utilizes the fact that the location of the off-center spectral peaks is dependent on the frequency of spatial modulation. Therefore, a single point of the maximum of the spectral peak can fully recover the undeformed taglines, as is evidenced by the overlap of the restored tagging grid with those taglines on the stationary tissues (Fig. 1). While the motion of the heart may slightly shift the center of the harmonic peak, such shift was insignificant in the current study because of the small region of heart in the overall FOV. Respiratory motion may also shift the center of the harmonic peak. However, it can be minimized by acquiring the images with respiratory gating.

Theoretically, undeformed tagging grid can be computed from tagging parameters. However, precise computation of the initial tagging grid requires gradient strength to be perfectly calibrated and phase errors to be corrected. As a result, such implementation becomes nontrivial. The current method has the advantage of being easy to implement without manual intervention. More importantly, the robustness of this method allows the restoration of an undeformed tagging grid from any tagged images in a cine series. Such robustness completely eliminates the requirements that a reference tagged image be acquired within the QRS complex, or at least as close as possible. Since multi-phase acquisition has the effects of reduced SNR and diminished tagging contrast, the current method will also benefit those studies that focus on the diastolic function of the heart by acquiring images during relaxation phase only.

Due to the requirement of extracting harmonic peaks in HARP analysis, 11 SPAMM tagging without higher order harmonic peaks is more desirable (15). However, 11 SPAMM tagging renders tag tracking more challenging because of the difficulty in resolving the thick taglines, especially at peak-systole and the end of diastole when significant tagline smearing and fading occur. The sharper taglines in higher-order SPAMM tagged images are more desirable for tag tracking when manual interference is necessary to resolve ambiguities.

1331 SPAMM tagging was used in the current study. The high tagging resolution led to sufficient separation of the harmonic peaks (Fig. 1a). As a result, HARP-based tagline tracking was effective and robust in most circumstances with an overall failing rate of ~5% that occurred at the apical and border regions. In the meantime, less tagline smearing was present at peak-systole.

In addition to tagline tracing, HARP-based methods have also been developed for fast and direct strain quantification (15,17,20). By calculating myocardial strain from the spatial derivatives of a HARP image, these methods eliminate the requirement for an undeformed reference grid. However, since taking derivatives of an image is more susceptible to inaccuracy associated with imaging noise, the accuracy of these methods in quantifying early systolic strain in mouse heart needs to be further investigated. Alternatively, displacement-encoded (DENSE) MRI also allows direct strain quantification without using a reference frame by directly encoding myocardial displacement in the phase images (22,23). This method has been applied in mouse imaging to evaluate the alteration in myocardial strain in post-infarct hearts (24). Typically, multi-acquisition is required to correct for phase errors in DENSE imaging.

While quantification of myocardial strain and torsion with MRI tagging can provide more comprehensive evaluation of ventricular function, it can also detect subtle changes in regional contractility that frequently manifests earlier than global functional alterations. However, inaccuracy in strain calculation may render such changes undetectable. In the current study, we compared our method to that without correction. Our results show that there was a significant underestimation of both strain and torsion if tagline deformation in the reference frame was not corrected (Fig. 6). As a result, it failed to detect a significant increase in circumferential strain during dobutamine stimulation. With a tagging module of ~7 ms, horizontally and vertically tagged images were acquired separately in our current study. If a tagging grid is acquired from a single acquisition, such inaccuracy can become more pronounced. Therefore, the inaccuracy of strain and torsion quantification can diminish subtle changes in ventricular contractile performance when comparing different animal models or different pathophysiological states.

The observed baseline function in the current study was consistent with that reported in the literature (4,5). Dobutamine stimulation led to increased heart rate and global function such as ejection fraction and wall thickening. These increases were similar to those reported in the earlier studies by cine MRI (11,12). In addition to enhanced global ventricular function, circumferential strain also increased significantly, accompanied by an increase in systolic strain rate. These observations were consistent with a recent MRI tagging study by Vansburger and colleagues (25). Comparing to changes in circumferential strain, increase in ventricular torsion (>50%) during β -adrenergic stimulation was much more pronounced, suggesting that torsion may be a more sensitive marker of changes in contractile performance (26–29). Further, our results suggest that increase in circumferential strain and LV torsion during dobutamine stimulation persisted throughout the entire systolic period.

In conclusion, we developed a HARP-based method to restore the undeformed taglines from a single point in the first-order harmonic peaks. Using this method, myocardial strain and torsion at early systole were quantified. Significant strain and torsion development was observed in dobutamine-stimulated hearts throughout systole. Our results also show that the calculated peak strain and torsion values were underestimated without correction for the deformation of taglines in the reference frame. Such underestimation diminished the contractile difference between dobutamine stimulated hearts and those at baseline working conditions.

Acknowledgments

Grant Support: National Heart, Lung, and Blood Institute

R01 HL-73315 and HL-86935 (To X. Yu)

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Figure 1. Tag tracking with HARP. **a.** harmonic peaks used for the tracking of deformed ($r=25$, yellow) and undeformed ($r=1$, magenta) tagging grids; **b&c.** π iso-contours generated from harmonic peaks extracted with a filter size of 25 (dotted yellow lines) and 1 (solid magenta lines) at early and end systole, respectively.

Figure 2. Myocardial deformation at early systole. **a.** circumferential strain; **b.** radial strain; **c.** twist angle. DOB, dobutamine stimulation. * $P < 0.05$, † $P < 0.01$ between baseline and dobutamine stimulation.

Figure 3. Time courses of ventricular twist (a) and torsion (b). * $P < 0.05$, † $P < 0.01$ between baseline and dobutamine stimulation.

Figure 4. Time courses of circumferential strain from apex to base. * $P < 0.05$, † $P < 0.01$ between baseline and dobutamine stimulation.

Figure 5.

Peak strain rate (a) and torsion rate (b) during systole and diastole. Solid bars: at baseline; open bars: under dobutamine (DOB) stimulation. †p<0.01 between baseline and dobutamine stimulation.

Figure 6.

Comparison of strain quantification with and without correction for deformed reference tagging grid. **a.** peak circumferential strain; **b.** peak radial strain. DOB, dobutamine stimulation. Solid and open bars are strains calculated with and without correction for tag deformation in the reference image, respectively. $^+P<0.05$, $^{\ddagger}p<0.01$ between baseline and dobutamine stimulation. $^*p<0.05$, $^{\S}p<0.01$ between with and without correction.