High-frequency speckle tracking echocardiography in the assessment of left ventricular function and remodeling after murine myocardial infarction

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Submitted 22 July 2013; accepted in final form 11 February 2014

Bhan A, Sirker A, Zhang J, Porrini A, Catibog N, Driver W, Botnar R, Monaghan MJ, Shah AM. High-frequency speckle tracking echocardiography in the assessment of left ventricular function and remodeling after murine myocardial infarction. Am J Physiol Heart Circ Physiol 306: H1371–H1383, 2014. First published February 15, 2014; doi:10.1152/ajpheart.00553.2013.—The objectives of this study were to assess the feasibility and accuracy of high-frequency speckle tracking echocardiography (STE) in a murine model of myocardial infarction (MI). STE is used clinically to quantify global and regional cardiac function, but its application in mice is challenging because of the small cardiac size and rapid heart rates. A high-frequency micro-ultrasound system with STE (Visualsonics Vevo 2100) was compared against magnetic resonance imaging (MRI) for the assessment of global left ventricular (LV) size and function after murine MI. Animals subjected to coronary ligation (n = 46) or sham ligation (n = 27) were studied 4 wk postoperatively. Regional and global deformation were also assessed. STE-derived LV ejection fraction (EF) and mass correlated well with MRI indexes (r = 0.93, 0.77, respectively; P < 0.001), as did STE-derived mass with post-mortem values (r = 0.80, P < 0.001). Higher STE-derived volumes correlated positively with MRI-derived infarct size (P < 0.01). Global strain parameters were significantly reduced after MI (all P < 0.001) and strongly correlated with LV mass and MRI-derived infarct size as promising surrogates for the extent of remodeling and infarction, respectively (both P < 0.05). Regional strain analyses showed that radial strain and strain rate were relatively preserved in anterior basal segments after MI compared with more apical segments (P < 0.001); however, longitudinal strain and strain rate were significantly impaired both basally and distally (P < 0.001). Strain-derived parameters of dyssynchrony were significantly increased in the MI group (P < 0.01). Analysis time for STE was 210 ± 45 s with acceptable inter- and intraobserver variability. In conclusion, high-frequency STE enables quantitative assessment of regional and global function in the remodeling murine LV after MI.

COMPARSED WITH CLINICAL IMAGING, echocardiography in mouse models remains relatively challenging, primarily because of the exceptional spatial and temporal resolution required to image such a small, rapidly beating heart. Research studies involving gene-modified mouse models commonly use clinical echocardiography systems (with transducer frequencies of up to 15 MHz) and tend to rely on rather simple measures of LV size and function, for example from M-mode tracings. These measures provide relatively crude estimates of global LV size and function, especially in remodeled hearts (e.g., after MI) where the geometric assumptions of symmetry are likely to be inaccurate. In clinical practice, such measures have largely been superseded, and the last decade has seen the introduction of several advanced echocardiography techniques to improve quantification of LV structure and function (5, 15, 18, 30).

Myocardial deformation (strain) imaging is one of the more robust of such techniques, having been extensively investigated clinically (4, 5, 15). It offers enhanced quantification of global as well as regional function, both of which are important in assessment of the remodeling LV. Deformation information can be derived either from color-coded tissue Doppler imaging or from 2-dimensional (2D) STE. STE uses patterns resulting from acoustic interference phenomena within the myocardium to track myocardial motion throughout the cardiac cycle (8, 17). The main advantage of STE over the Doppler-based technique is its lack of dependence on the ultrasound insonation angle (10). This may be of particular benefit in small animal imaging where the ability to align myocardial structures of interest with the transducer can be challenging.

Recent advances in high-frequency micro-ultrasonography have led to the commercial availability of a dedicated small animal ultrasound system equipped with a high-frequency transducer (Vevo 2100, Visualsonics, Toronto, Canada) that allows quantification of global and regional LV function with speckle tracking-derived measurements. We evaluated the utility of ST-based assessment of global and regional LV function in mice undergoing LV remodeling after left coronary ligation or sham surgery. The study had three specific aims: 1) to compare data for LV volumes, ejection fraction, and mass (which are automatically obtained during STE analysis) against the reference standard of MRI; 2) to assess parameters of global deformation and their relationship to infarct size and LV mass (as a measure of extent of remodeling); and 3) to assess regional deformation and LV dyssynchrony after MI.

MATERIALS AND METHODS

Surgery and general protocol. In vivo procedures were conducted in accordance with the Guidance on the Operation of the Animals (Scientific Procedures) Act, 1986 (UK Home Office), and with the approval of the local independent institutional review committee. A total of 73 adult female C57Bl6 mice (weight 18–24 g) were studied, either after left coronary ligation (n = 46) or sham surgery (n = 27). Animals were anesthetized with 2–2.5% isoflurane/97.5–98% oxygen, endotracheally intubated, and ventilated using a small animal ventilator (Hugo Sacks Elektronik, Germany). Myocardial infarction was created, in a similar manner to that previously described by our group (13). However, a wider range of infarct sizes was produced in the...
present study, by ligating the left coronary artery at varying levels below the left atrial lower border; this permitted a broad range of subsequent left ventricular volumes and dysfunction to develop and be comparatively evaluated using echocardiography vs. MRI. Sham surgery involved an identical procedure except for coronary ligation. Animals were administered buprenorphine and flunixin analgesia and allowed to recover in a warmed chamber. Four weeks (± 2 days) after surgery, all mice underwent transthoracic echocardiography and magnetic resonance imaging (MRI), the two modalities being performed within 24 h of each other. After animals were killed, hearts were excised, the LV was dissected, and LV mass was measured using a fine balance.

**Echocardiography.** Transthoracic echocardiography was performed using the Vevo 2100 ultrasound system (Visualsonics, Toronto, Canada) equipped with a high-frequency (30 MHz) linear array transducer. Animals were placed supine on an electrical heating pad at 37°C under light isoflurane anesthesia (usual maintenance level 1.5% isoflurane/98.5% oxygen). Continual ECG monitoring was obtained via limb electrodes. Heart rates were >450 beats/min for the duration of the study (with adjustment of level of anesthesia as necessary). Any

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**Fig. 1.** Representative images of speckle tracking echocardiography (STE)-based analyses of ventricular function. **A**: an example of the semiautomated endocardial and epicardial border detection in a parasternal long-axis view. **B**: segmental radial and longitudinal strain curves from a parasternal long-axis view in a mouse after myocardial infarction.
images obtained with suboptimal physiological parameters were excluded from analysis.

A 2D echocardiographic study was performed predominantly in parasternal long-axis except where noted otherwise. Careful attention was paid to image depth, width, and gain settings in order to optimize image quality. Frame rates were consistently above 150 Hz with a mean of 201 Hz (±24). All views were digitally stored in cine loops consisting of 300 frames. Subsequent analysis was performed off-line on a workstation installed with Vevo 2100 software (version 1.4.0) by two experienced cardiologists blinded to the surgery type. Analyses of LV volumes and ejection fraction (EF) were performed using both the standard 2D quantification software and the dedicated STE software.

For standard 2D analyses, the user marks out the endocardial border in end-diastole and end-systole. The software places an imaginary trapezoid around the LV, then calculates the difference between the traced border and the trapezoid using a method of disks technique. This is subtracted from the known volume of the trapezoid to obtain LV volumes. To calculate mass using the standard technique, borders were traced along the endocardium and epicardium and mass was calculated from these using the area-length method (33).

Analyses in the STE software utilize semiautomated border tracking. First, the user places a number of tracking points on the endocardial and epicardial borders. These are used as a guide for border delineation and subsequent frame-by-frame tracking throughout the cardiac cycle (Fig. 1A). From these borders and their motion, LV volumes are calculated using a method of disks technique (25), and ejection fraction is subsequently obtained. Manual adjustments can be made as required in order to optimize border tracking. During STE

![Fig. 2. Comparison of end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF) assessed by STE vs. MRI. A, C, E: linear correlations of the volumetric parameters assessed by STE vs. MRI. The 95% confidence band of the regression lines is enclosed by dotted lines. B, D, F: Bland-Altman analyses for each parameter. Dotted lines show the best estimate of bias as well as its limits of agreement (LoA).](http://ajpheart.physiology.org/)

Innovative Methodology

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AJP-Heart Circ Physiol • doi:10.1152/ajpheart.00553.2013 • www.ajpheart.org

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analysis, the LV is automatically divided into six segments. For the parasternal long-axis view, this means two basal, two mid, and two apical segments. Strain curves are made available for each analyzed segment (Fig. 1B), without the requirement for any additional user input. LV mass is calculated from the difference between the endocardial and epicardial borders at end diastole, and the myocardial density constant. Data were obtained for LV volumes, EF, LV mass, peak longitudinal and radial segmental strain (S) and strain rate (SR), and the time to peak strain (time from the onset of the QRS complex to peak strain value). The standard deviation of time to peak strain, corrected for the RR interval, was used as a measure of intraventricular dyssynchrony (34).

**Magnetic resonance imaging.** MRI was performed in a 7-T horizontal scanner (Varian, Palo Alto, CA) with a gradient coil inner diameter of 12 cm, 1000 mT/m (100 G/cm) strength, and rise-time of 120 μs. A quadrature transmit/receive coil (RAPID Biomedical) with an internal diameter of 39 mm was used. Anesthesia and physiological parameters were maintained as for echocardiography. Eleven short-axis slices were acquired from apex to base of the left ventricle with an in-plane resolution of 0.195 × 0.195 mm and a slice thickness of 1 mm. MRI acquisitions were performed over a period of ~8 min per animal and this was comparable to that for echocardiography. Off-line analyses of LV volumes, EF, and mass from MRI were performed using a semiautomated software program developed in-house (22). This calculated the left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) after estimating end-diastolic and end-systolic blood pool volumes for each MRI slice. The software also identified epicardial borders from which LV mass could be calculated as the end-diastolic LV myocardial volume multiplied by an MRI density factor (1.055 g/cm³). For the subgroup...
of mice in which infarct size was estimated, this was done from the 11 consecutive short-axis views from base to apex. The infarct size was calculated as the percentage midline length of thinned myocardium against the total LV midline length (21, 22). Thinned myocardium was defined as a reduction in thickness by >60% compared with healthy myocardium, and the motionless properties of the tissue in MRI images during the cardiac cycle. Our group and others have previously demonstrated good agreement with histologically determined infarct size using triphenyltetrazolium chloride (TTC) staining (22).

Intra- and interobserver variability. Blinded repeat analyses of echocardiographic data from 20 randomly chosen studies were performed at an interval of several weeks by the original observer and a different observer, in order to obtain inter- and intraobserver variability (n = 8 and n = 12, respectively). To assess test-retest variability, in seven animals we undertook two echocardiograms 24 h apart.

Statistics. Data are presented as means ± standard error of the mean (SE). A Student’s t-test was performed for comparison of continuous variables between the groups. P < 0.05 was considered statistically significant. Correlations were assessed using linear regression and correlation coefficients, and agreements between measures were shown using Bland-Altman plots. Variability is reported as the mean (± SD) of the absolute differences between paired measurements and by the correlation coefficient (r). All statistical analyses were performed using Graphpad Prism v4 (Graphpad Software).

RESULTS

LV volumes, mass, and global function. A comparison of STE-derived LV end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF) against MRI was performed on the entire cohort of 73 mice. This demonstrated

![Diagram](http://ajpheart.physiology.org/)

Fig. 4. Comparison of STE-derived vs. MRI-derived and necropsy LV mass (LVM). The dotted lines on the regression graphs (A, C, E) showed the 95% confidence band of the regression. Dotted lines on the Bland-Altman plots (B, D, F) show the best estimate of bias and the limits of agreement (LoA).
a good correlation between STE and MRI for all parameters, with \( r \) values between 0.86 and 0.93 (all \( P < 0.0001 \) for all) (Fig. 2). There was, however, a significant underestimation of all three parameters by STE with biases (average differences between MRI and STE) of 7.82 \( \mu \)l, 3.75 \( \mu \)l, and 4.78\% for LVEDV, LVESV, and EF, respectively. Heart rates were not significantly different between the MI and sham groups (495 \( \pm \) 30 and 479 \( \pm \) 44 beats/min, \( P = 0.39 \)). The mean EF using STE-derived data was 54.0 \( \pm \) 1.3\% in the sham group vs. 22.5 \( \pm \) 1.4\% in the MI group (\( P < 0.0001 \)).

We also compared standard 2D-derived parameters against MRI in the same cohort (Fig. 3). 2D-derived EDV, ESV, and EF also correlated quite well with MRI-derived data but with slightly lower correlation coefficients (0.84 to 0.89) than for STE-derived measures. Bland-Altman plots demonstrated larger biases with 2D measures than STE-derived measures, and these were less systematic: e.g., positive bias for EDV and negative bias for ESV.

In a subgroup of 14 animals (7 sham, 7 MI), STE- and MRI-derived LV mass estimation were compared against each other and against the necropsy mass (Fig. 4). STE-derived mass correlated well with MRI (\( r = 0.77, P = 0.0007 \)) and necropsy mass (\( r = 0.80, P = 0.0003 \)), while MRI-derived mass also correlated with necropsy measures (\( r = 0.74, P = 0.0037 \)). Mass by STE was slightly underestimated compared with necropsy mass (estimate of bias = 9.17 mg), while MRI-derived results were closer in value to necropsy mass (estimate of bias = 1.00 mg). Using STE-derived data, LV mass was 56.5 \( \pm \) 3.0 mg in the sham group vs. 97.9 \( \pm \) 4.7 mg in the infarct group (\( P < 0.0001 \)).

In a subset of 20 MI animals, we estimated in vivo infarct size from consecutive short-axis MRI images as described in MATERIALS AND METHODS and then assessed the correlation between infarct size and STE-derived volumetric parameters. There was a significant linear correlation between MRI infarct size and LV volumetric parameters obtained by STE in this group; i.e. EDV (\( r = 0.75, P = 0.0005 \)), ESV (\( r = 0.82, P < 0.0001 \)), and EF (\( r = -0.81, P < 0.0001 \)) (Fig. 5). Infarct size correlated with necropsy mass (as a parameter of total LV remodeling, i.e., amount of hypertrophy in remote myocardium), as would be expected (Fig. 5).

Taken together, these results suggest that STE-derived volumetric parameters provide useful measures of adverse LV remodeling after MI in mice.

**Global strain parameters of myocardial deformation.** We next analyzed strain parameters in 35 mice (10 sham, 25 MI). Global peak strain (PS) and strain rate (PSR) were derived by taking the mean of all 6 analyzed segments in longitudinal and radial directions (Fig. 1B). Both longitudinal and radial global strain and the corresponding strain rates were significantly lower in the MI group vs. sham controls (Fig. 6). In a subset of 14 MI mice where both postmortem LV mass and strain data were available, LV mass as a simple measure of total LV remodeling correlated negatively with parameters of both longitudinal and radial strain (Fig. 7). This correlation was stronger for longitudinal strain and strain rate than for radial strain/strain rate.

In a subset of seven MI animals, we assessed global strain parameters both from a conventional parasternal long-axis view (involving 6 segments; Fig. 1) and from consecutive
short-axis views from base to apex (i.e., involving all 16 LV segments). Both sets of global strain parameters were significantly correlated with MRI-derived infarct size (Fig. 8). In general, global strain derived from short-axis views showed slightly better correlation with infarct size than that based on a long-axis view (e.g., radial strain \( r = -0.81 \) vs. \( r = -0.63 \)).

**Regional myocardial strain.** Regional deformation was analyzed on a segmental basis (3 anterior and 3 posterior segments) in a subset of 31 animals (14 sham, 17 MI). The mean peak radial strain per segment was significantly lower in MI compared with sham hearts for all segments except the anterior basal segment (Fig. 9). Anterior mid and apical segments showed reduced strain in MI hearts compared with sham as did all three posterior segments. A similar pattern held true for radial strain rate. Longitudinal strain and strain rate, however, were reduced in all segments of MI hearts compared with sham. For all four strain parameters, the apical segments in MIs had lower peak strain/strain rates compared with mid and basal segments, corresponding to the apical location of infarct regions secondary to LAD occlusion.

**LV dyssynchrony.** The data for radial and longitudinal strain and corresponding strain rates that was used for global strain analysis above (i.e., 35 mice: 10 sham, 25 MI) were also analyzed for dyssynchrony. This showed that the standard deviation of the time to peak strain (corrected for the RR interval) was significantly higher in the MI group compared with sham for all four parameters (Fig. 10A). Radial intraventricular strain dyssynchrony was 20.4 ± 2% in the MI group vs. 8.5 ± 1.4% in shams, while longitudinal strain dyssynchrony was 16.6 ± 2.2% in the MI group vs. 7.5 ± 1.3% in shams (\( P < 0.01 \) for all comparisons). The dyssynchrony index

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Fig. 6. Differences in global strain [longitudinal (A) and radial (C)] and strain rate [longitudinal (B) and radial (D)] between MI and control groups. **\( P < 0.005 \), ***\( P < 0.0001 \) by unpaired t-test.

Fig. 7. Linear regression of global strain (A, C) and strain rates (B, D) against postmortem LV mass (LVM) in infarcted hearts. The dotted lines show the 95% confidence range of the regression line.
Fig. 8. Linear regression of global strain/strain rate derived from parasternal long-axis views (PSLAX) or sequential short-axis views (SAX) from base to apex against MRI-derived infarct size. The dotted lines show the 95% confidence range of the regression line.
correlated positively with MRI-derived infarct size for all strain parameters (Fig. 10B); i.e., larger infarcts were associated with greater dyssynchrony.

Analysis time, and inter- and intraobserver and test-retest variability. The total offline analysis time required to obtain LV volumes, EF, LV mass, and regional strain curves was 3.5 ± 0.75 min per study for echocardiography. MRI analysis time for volumes and mass was 9 ± 2 min per study. Data for inter- and intraobserver variability and test-retest variability are shown in Table 1. These analyses show acceptable inter- and intraobserver and test-retest variability for most indexes. Estimation of dyssynchrony index was more reproducible when using strain than strain rate.

DISCUSSION

Despite significant recent advancements in clinical echocardiography, studies in gene-modified mouse models generally employ relatively basic echocardiographic imaging methods and analyses with only a few exceptions (24). This is in stark contrast to the complex and innovative molecular biological techniques that are commonly used to create these models. In this study, we have undertaken a careful evaluation of STE-based imaging in mice using a dedicated high-frequency small animal ultrasound system. We focused on mice undergoing adverse LV remodeling after permanent coronary ligation, a commonly used experimental model that is challenging for accurate estimation of LV volumes and mass from (1D) M-mode or 2D echocardiography due to the irregular geometric shape of the remodeled LV. Our results indicate that STE-based assessment of global LV volumes and function as well as regional function in mice is fast, simple, and reproducible, compares favorably with MRI, and is suitable for the assessment of LV remodeling after MI.

The STE-based quantification of parameters of global LV structure and function (i.e., LV volumes, mass, and EF) were automatically calculated by the software when performing a deformation analysis, and therefore required minimal additional operator input. STE-derived parameters measured in this manner correlated very well with MRI-derived measures in the same animals. Furthermore, there was a good linear correlation between infarct size and STE-derived measures of LV dilatation and LV function (as would be expected from first principles), indicating that the technique can be applied across a group of mice with variable degrees of infarction and LV remodeling and provides biologically sensible data in this setting. STE-derived LV volumes and mass underestimated the values obtained by MRI. In the context of volumes, because both ESV and EDV were generally underestimated, the EF data were closer to the corresponding MRI values. Assessment of LV volumes and mass by standard 2D-echocardiography also correlated with MRI data, but there were larger biases than with STE-derived measures. This may at least in part reflect the
different algorithms that were employed for STE vs. standard 2D-derived measures (see MATERIALS AND METHODS). A similar underestimation of LV volumes by STE compared with 3D echocardiography or MRI is also reported in human studies (14, 15). The underestimation is most probably a result of foreshortening of the true LV long axis and inaccuracies caused by geometrical assumptions. In addition, difficulty in differentiating trabeculations from the true endocardial boundary also plays a role. Therefore, MRI remains the gold standard for absolute quantification of LV volumes but STE-derived measures may have significant utility in serial assessment and for comparison among groups. Another clear advantage of MRI remains the direct determination of infarct size, which is often critical in experimental models in ensuring equal stimuli to postinfarct LV remodeling across different study groups (21, 22). On the other hand, echocardiography has a number of other potential benefits over MRI, namely 1) greater availability to researchers in many institutions; 2) greater tolerability—

Fig. 10. Dyssynchrony derived from strain and strain rates. A: comparison of dyssynchrony derived from longitudinal and radial strain and strain rates between MI and sham control groups. **P < 0.005; ***P < 0.0001. B: linear regression of strain-derived dyssynchrony against MRI-derived infarct size.
some groups even use echo in conscious mice that have undergone training in order to allow this (32), whereas the remote positioning of mice far from the experimenter during MRI renders this impractical in MRI scanning; 3) better frame rates during scanning (in the present study, typically around 200 Hz for echocardiography vs. 83 Hz for MRI), permitting increased confidence in correctly acquiring end-diastolic and end-systolic time points; 4) lower equipment costs; 5) portability, allowing its use as an adjunct to other experiments, e.g., during pressure-volume loop assessment using conductance catheterization, echo can be used to allow calibration of volume in absolute terms by performing simultaneous measurement of LV cavity size on echo (while the conductance catheter is in place and measuring volume). This could not be achieved using MRI due to fixed nature of the equipment, issues relating to the magnetic field, and the remote positioning of the experimental animal in the scanner.

A second aim of our study was to investigate parameters of global deformation. STE-derived deformation data readily differentiated between infarcted mice and control animals. More importantly, global strain parameters correlated well with MRI-derived infarct size or postmortem LV mass, as a determinant and a simple measure of the degree of LV remodeling, respectively. In other words, larger infarcts and hearts with higher mass (more remodeling) were associated with lower strain. Although global strain parameters derived from consecutive short-axis views which involved 16 segments showed slightly higher correlation with infarct size than those based on a single long-axis view involving 6 segments, strong correlations were still found in the latter case. Therefore, data based on a single long-axis view provide useful information but can be extended to a more time-consuming analysis involving multiple short-axis views. Clinical data show similar relations between global strain and abnormal LV function. For example, a recent study in patients with hypertrophic cardiomyopathy (HCM) that compared STE and delayed hyperenhancement MRI found a correlation between global longitudinal strain and the number of fibrotic segments, as well as total LV hypertrophy (19). Furthermore, Peng et al. (16) reported that circumferential strain accurately tracks the progression of heart failure induced by transaortic constriction in mice and that it was reflective of myocardial fibrotic changes. Whether the relationship observed between longitudinal strain and LV mass may also, in part, be attributable to the presence of myocardial fibrosis requires further study. Strain rate has also been shown to be useful in the assessment of transmurality of MI early after reperfusion or at follow up (29, 31, 35).

Regional assessment is an important application of strain, and this has been validated in humans (3, 7, 8). Regional function was assessed in our study by comparing myocardial deformation at six different segments involving anterior and posterior walls. Comparison of mean strain from these segments revealed that radial strain parameters were relatively well preserved at the anterior basal wall of infarcted hearts compared with more distal regions, consistent with these segments being remote from the infarct. However, longitudinal strain was significantly impaired in basal segments as well as more distal ones, suggesting that it may be a more sensitive marker of subtle changes in function. Indeed, changes in longitudinal strain are among the first parameters to be affected during cardiac remodeling (6, 9, 23). Longitudinal strain is more sensitive than radial strain in acute and chronic ischemia in humans (6). In patients with hypertensive heart failure, longitudinal strain is impaired in those with milder symptoms whereas radial parameters are only affected with more severe limitation (9). The increased sensitivity of longitudinal strain may be related to the fact that longitudinal function is largely a result of endocardial fiber motion, which is altered earlier during postischemic remodeling. It is reported, however, that the relative contribution of long-axis function may be lower in small mammals than humans (20), and this is an interesting area for future studies. Interestingly, posterior basal segments (which are remote from the infarct) showed reduced radial as well as longitudinal strain compared with sham animals. This may reflect the complexity of the LV remodeling that occurs after MI in the mouse permanent ligation model, being influenced both by the regional properties of the myocardium (e.g., hypertrophy, fibrosis, contractile function) and by interactions among segments. Comparison with other studies after mouse MI is difficult because previous work either only reported strain measured in a single short-axis slice (28), or studied reperfused MI (11, 12). However, Li et al.

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Table 1. Inter- and intraobserver variability for measured parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean difference (SD)</th>
<th>Correlation</th>
<th>Mean difference (SD)</th>
<th>Correlation</th>
<th>Mean difference (SD)</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard EDV, µl</td>
<td>6.9 (18.2)</td>
<td>0.94</td>
<td>4.3 (19)</td>
<td>0.93</td>
<td>7.3 (19.2)</td>
<td>0.87</td>
</tr>
<tr>
<td>Standard EF, %</td>
<td>2.3 (4.1)</td>
<td>0.95</td>
<td>4.8 (4.3)</td>
<td>0.89</td>
<td>5.2 (5.1)</td>
<td>0.90</td>
</tr>
<tr>
<td>Standard LVM, mg</td>
<td>4.6 (14.6)</td>
<td>0.93</td>
<td>17 (18.6)</td>
<td>0.88</td>
<td>14 (16.2)</td>
<td>0.88</td>
</tr>
<tr>
<td>STE EDV, µl</td>
<td>2.7 (17.2)</td>
<td>0.94</td>
<td>3.6 (22.2)</td>
<td>0.94</td>
<td>1 (10.1)</td>
<td>0.92</td>
</tr>
<tr>
<td>STE EF, %</td>
<td>2.6 (2)</td>
<td>0.93</td>
<td>4.8 (3.4)</td>
<td>0.94</td>
<td>3.8 (4)</td>
<td>0.91</td>
</tr>
<tr>
<td>STE LVM, mg</td>
<td>3.3 (12.3)</td>
<td>0.94</td>
<td>5.4 (14.3)</td>
<td>0.94</td>
<td>4.6 (15.2)</td>
<td>0.92</td>
</tr>
<tr>
<td>Global radial strain, %</td>
<td>0.8 (1.1)</td>
<td>0.98</td>
<td>0.7 (1.7)</td>
<td>0.94</td>
<td>1.7 (3.1)</td>
<td>0.85</td>
</tr>
<tr>
<td>Radial strain DI, %</td>
<td>0.9 (3.4)</td>
<td>0.90</td>
<td>1.8 (8.1)</td>
<td>0.82</td>
<td>2 (7.2)</td>
<td>0.81</td>
</tr>
<tr>
<td>Radial strain rate, %/s</td>
<td>1.1 (0.9)</td>
<td>0.92</td>
<td>1.2 (1.7)</td>
<td>0.83</td>
<td>0.3 (1.1)</td>
<td>0.82</td>
</tr>
<tr>
<td>Radial strain rate DI, %</td>
<td>2.5 (7.3)</td>
<td>0.68</td>
<td>2 (13.5)</td>
<td>0.71</td>
<td>1.3 (12.4)</td>
<td>0.78</td>
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<tr>
<td>Global longitudinal strain, %</td>
<td>1.4 (1.9)</td>
<td>0.96</td>
<td>0.8 (2.7)</td>
<td>0.90</td>
<td>0.6 (1.8)</td>
<td>0.86</td>
</tr>
<tr>
<td>Longitudinal strain DI, %</td>
<td>4.2 (10.2)</td>
<td>0.74</td>
<td>6.6 (12.9)</td>
<td>0.69</td>
<td>1.8 (7.2)</td>
<td>0.79</td>
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<tr>
<td>Longitudinal strain rate, %/s</td>
<td>1.8 (1.1)</td>
<td>0.85</td>
<td>3.2 (2.3)</td>
<td>0.81</td>
<td>0.4 (1.6)</td>
<td>0.82</td>
</tr>
<tr>
<td>Longitudinal strain rate DI, %</td>
<td>3.7 (9.9)</td>
<td>0.68</td>
<td>5.2 (9.7)</td>
<td>0.64</td>
<td>3.1 (7.2)</td>
<td>0.76</td>
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</tbody>
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EDV, end-diastolic volume; EF, ejection fraction; LVM, left ventricular mass; PS, peak strain; PSR, peak strain rate; STE, speckle tracking echocardiography; longit., longitudinal; DI, dysynchrony index
(12) reported significant reduction in regional function in remote segments after reperfused MI, which might be expected to be even worse after permanent coronary ligation. It would be useful in future studies to compare STE-derived strain data with MRI-derived measures, which was not possible in the current study for technical reasons.

LV intraventricular dyssynchrony is an important therapeutic target in humans, and its assessment by echocardiography is topical. Methods that have been proposed in clinical practice include tissue Doppler imaging and STE (28, 34). The potential advantage of STE over tissue Doppler, especially in murine imaging, is its lack of dependence on the angle of incidence of the ultrasound beam (27). In the current study, STE-based measures of dyssynchrony reliably differentiated between animals with MI and controls. Furthermore, the extent of dyssynchrony correlated positively with infarct size. To our knowledge, this is the first study to use a commercially available software package designed for small animal imaging to assess LV dyssynchrony in mice. Other studies have reported on LV dyssynchrony measured with a commercially available system in a canine model (1). We show that assessment of LV dyssynchrony with the current system is straightforward in mice although additional studies are required to assess the reliability of such data in more detail. It is likely that data fidelity would be improved by averaging peak values over a number of cardiac cycles, which was not done in the current study. Other technical issues that may impact on the applicability of the technique include the ability to define peak strain values in infarcted segments with flattened strain curves, the definition of timing of aortic valve opening and closure, and limitations concerning maximal frame rates.

The absolute values that we obtained for strain and strain rate appear to be lower than other published data (11, 26). In their paper from 2005, Sebag et al. (26) used color-coded tissue Doppler imaging to assess myocardial velocities and strain rates in mice at rest and during infusions of esmolol and dobutamine. They were only able to assess radial deformation but obtained radial strain rates in resting mice of around 12 s⁻¹. Li et al. (11) assessed radial and circumferential strain in normal and post-MI mice using custom STE software and obtained radial strain values of up to 40% in normal mice. When directly comparing these results to our findings, several important issues should be considered. First, results using different techniques and different software packages cannot necessarily be extrapolated from one to another. Second, the values may be significantly affected by differences in animal sedation and heart rates. Third, one important trade-off for the angle independency of STE is a more limited frame rate capability. While a frame rate of ≥150 Hz is suggested by the manufacturer to be sufficient for reliable data, different frame rates could affect the absolute values of strain. In a recently published study using an identical system to that employed in our work, Bauer et al. (2) reported mean longitudinal and radial strain and strain rates in control mice that were similar to our results. In their sham-operated animals they found mean longitudinal strain and strain rate to be -15.7% and -7.4 s⁻¹, respectively, compared with -15.3% and -6.6 s⁻¹ in our study. Mean radial strain and strain rate derived from their long-axis images were 19.4% and 8 s⁻¹, respectively, compared with our findings of 17.1% and 5.5 s⁻¹. These authors also studied mice after MI and found mean longitudinal strain and strain rate to be -3.4% and -2.3 s⁻¹ compared to our values of -5.7% and -2.5 s⁻¹, respectively. These figures for radial deformation were 8% and 5.2 s⁻¹ for Bauer et al. and 9.1% and 3.6 s⁻¹ in our animals. Their follow up scans, however, were performed at time intervals different from ours (3 wk rather than 4) making a direct comparison of these results a little more difficult. In general, strain data of the type reported here are probably best compared with measures that use identical systems and similar anesthetic protocols.

The present study indicates that high-frequency 2D STE offers reliable and reproducible assessment of both global and regional function in post-MI remodeling mouse hearts, involving relatively straightforward and rapid analysis with dedicated software. STE-derived parameters of global LV structure and function correlate well with the noninvasive gold standard of MRI and appear suitable for distinguishing among varying extents of adverse LV remodeling and function. In addition to the traditional measures of LV structure and function, we confirm the feasibility of obtaining detailed STE-based data on global and segmental deformation. STE-based noninvasive assessment of cardiac structure and function therefore has the potential to significantly enhance studies investigating LV remodeling in mouse models.

GRANTS
This work was supported by The British Heart Foundation (BHF) and the Fondation Leducq. A. Sirker was funded by a British Cardiovascular Society Prize Fellowship.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

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