Published in final edited form as:

Ultrasound Med Biol. 2011 July ; 37(7): 1073–1086. doi:10.1016/j.ultrasmedbio.2011.04.002.

SERIAL ULTRASOUND EVALUATION OF INTRAMYOCARDIAL STRAIN AFTER REPERFUSED MYOCARDIAL INFARCTION REVEALS THAT REMOTE ZONE DYSSYNCHRONY DEVELOPS IN CONCERT WITH LEFT VENTRICULAR REMODELING

Yinbo Li*, Christopher D. Garson*, Yaqin Xu*, Patrick A. Helm†, John A. Hossack*, and Brent A. French*,†,‡

*Department of Biomedical Engineering, University of Virginia, Charlottesville, VA, USA

†Radiology, University of Virginia, Charlottesville, VA, USA

‡Medicine, University of Virginia, Charlottesville, VA, USA

Abstract

This study noninvasively evaluated the development of left ventricular (LV) dyssynchrony following reperfed myocardial infarction (MI) in mice using an ultrasonic speckle-tracking method. Eight C57BL/6J mice were assessed by high-resolution echocardiography at baseline and at eight time-points following MI. Images were acquired at 1mm elevational intervals encompassing the entire LV to determine chamber volumes and radial strain. Receiver-operating characteristic (ROC) analysis of regional radial strain was used to segment the three-dimensional (3-D) LV into infarct, adjacent and remote zones. This *in vivo* segmentation was correlated to histologic infarct size ($R = 0.89$, $p < 0.01$) in a short-axis, slice-by-slice comparison. The onset of dyssynchrony during LV remodeling was assessed by standard deviation of time to peak radial strain in the infarct, adjacent and remote zones. It was discovered that the form of LV dyssynchrony that develops in the remote zone late after MI does so in concert with the progression of LV remodeling ($R = 0.70$, $p < 0.05$).

Keywords

Myocardial infarction; Cardiac dyssynchrony; Left ventricular remodeling; High resolution ultrasound

INTRODUCTION AND LITERATURE

Heart failure resulting from myocardial infarction (MI) continues to represent a costly and prevalent medical challenge to world health, particularly in older patients. Indeed, recent data indicate that 20% of patients over 70 develop heart failure within 5 years of new MI (Lloyd-Jones et al. 2010).

Over the past decade, left ventricular (LV) dyssynchrony has become increasingly recognized as an important contributor to the pathophysiology of heart failure (Bader et al. 2004; Cho et al. 2005). Clinical trials examining LV dyssynchrony in heart failure typically

include the endpoints of electrical dyssynchrony (as defined by a widened QRS interval) and mechanical dyssynchrony (as defined by echocardiography or cardiac magnetic resonance imaging). Cardiac resynchronization therapy (CRT) is currently favored for the treatment of LV dyssynchrony but it is only effective in approximately 2/3 of patients that meet the current guidelines (*i.e.*, New York Heart Association [NYHA] functional class III or IV heart failure with left ventricular ejection fraction [LVEF] <35% and wide QRS complex [Strickberger et al. 2005]). This low success rate, combined with the costly and invasive nature of CRT, created an urgent need for more accurate methods for identifying patients that will respond positively to CRT. Although the results of the Predictors of Response to CRT (PROSPECT) trial would appear to suggest that the echocardiographic analysis of mechanical LV dyssynchrony is only modestly effective in predicting response to CRT, this finding was subsequently challenged (Bax and Gorcsan 2009) and more recent trials using improved echocardiographic methods now indicate that mechanical indices of dyssynchrony can add significant prognostic power to predictive models that include QRS duration (Cho et al. 2010; Porciani et al. 2010). Based on these studies and others, one can predict that improved echocardiographic equipment and analysis packages, combined with more accurate metrics of mechanical LV dyssynchrony, will ultimately prove quite valuable in helping to select patients for CRT. In particular, the combination of speckle-tracking for radial strain determination and dyssynchrony metrics including: (1) difference between time to peak-systolic strain of the anteroseptal and posterior segments and (2) the standard deviation of time to peak strain (SD_T_{peak}) would appear to be quite promising in this regard (Delgado et al. 2008).

Independent of the ongoing debate regarding the selection of candidates for CRT, data from the Valsartan in Acute Myocardial Infarction Trial (VALIANT) (Shin et al. 2010) recently demonstrated that, after MI, LV dyssynchrony is independently associated with an increased risk of death or heart failure. This finding is entirely consistent with biomechanical models of heart failure that suggest that the progression of heart failure may be a result of positive feedback between LV remodeling and cardiac dysfunction (including dyssynchrony) (Mann 1999; Mann and Bristow 2005). In recent years, a series of clinical studies have established that mechanical LV dyssynchrony, measured shortly after MI, predicts the extent of subsequent LV remodeling (Mollema et al. 2007; Chang et al. 2009). However, the temporal evolution of LV dyssynchrony after MI remains to be elucidated and directly compared with the evolution of LV remodeling. Furthermore, better methods are needed to distinguish between the early form of dyssynchrony that occurs in the infarct region shortly after MI and the form of dyssynchrony that develops much later in the remote, noninfarcted LV.

Post-infarction LV remodeling can be classified into distinct phases, including an early infarct expansion phase, followed by infarct extension into adjacent noninfarcted myocardium (Jackson et al. 2002) and late hypertrophy and fibrosis in the remote LV (Sutton and Sharpe 2000; French and Kramer 2007). Although its time course has not been explicitly defined, cardiac dyssynchrony evolves from an early stage with initial insult in the infarct zone to a late stage involving the entire LV, with dyssynchrony afflicting the remote zone as well as the infarct zone. Immediately after MI, systolic bulging and contractile delay have been recognized locally in the infarct and adjacent zones (Akaishi et al. 1986; Noma et al. 1988). At the late stage of LV remodeling, contractile dyssynchrony is evident globally throughout the LV (Yu et al. 2002; Suffoletto et al. 2006). The progression of dyssynchrony may ultimately be linked to the escalating mechanical disadvantage resulting from the alterations in myocardial geometry and composition incurred during the LV remodeling process (Mann and Bristow 2005).

The current study was therefore undertaken with a two-fold purpose: (1) to better define the relationship between LV remodeling and LV dyssynchrony by measuring both endpoints in

a serial echocardiographic study of mice following reperfused MI and (2) to develop a metric capable of distinguishing between the dyssynchrony exhibited by subacute infarcts as opposed to that which develops late after MI in the remote zone. Toward this end, the evolution of LV dyssynchrony following MI was assessed throughout the three-dimensional (3-D) LV in three specific regions-of-interest (the infarct, adjacent and remote zones) by analyzing regional radial strain and its timing characteristics relative to the cardiac cycle. The SD_T_{peak} in the remote zone was then compared with the evolution of LV remodeling (as measured by LV end-systolic volume) to reveal that two endpoints are tightly linked during the LV remodeling process. Furthermore, a new metric for dyssynchrony was developed (contraction index, CI) that is particularly sensitive to the dyskinetic infarct zone early after MI. These quantitative assessments of the evolution of LV dyssynchrony should prove useful in probing the biomolecular mechanisms underlying the progression of left ventricular remodeling after MI and, thus, may ultimately help improve the diagnosis and treatment of heart failure.

MATERIALS AND METHODS

Animals and image acquisition

This study conformed to the Guide for the Care and Use of Laboratory Animals (NIH publication No. 85-23) and was conducted under protocols approved by the University of Virginia Animal Care and Use Committee. Male C57BL/6J mice (12–16-week-old) were employed in this study. MI was surgically induced in eight mice by 60 min occlusion of the left anterior descending (LAD) coronary artery followed by reperfusion as described previously (Yang et al. 2002). In brief, mice were anesthetized with sodium pentobarbital (50 mg/kg, intraperitoneally [IP]) and ventilated with an endotracheal tube. The chest was opened and coronary artery occlusion was achieved by passing a 7-0 silk suture beneath the LAD 2 to 3 mm inferior to the left auricle, then tightening it over a length of PE-20 tubing. After 60 min, the tubing was removed to achieve reperfusion and the chest was closed in layers. The endotracheal tube was removed once spontaneous breathing resumed. This technique reproducibly induces myocardial infarction in the apex and anterolateral walls of the mouse LV. Imaging was performed as described below. Within 24 h after the final scan, the mice were euthanized for infarct size determination using 2,3,5-triphenyl tetrazolium chloride (TTC) (Ross et al. 2002). After staining, the mouse heart was cut transversely into five to six short-axis slices, each 1 mm thick. Digital photomicrographs (Olympus SZX1; Tokyo, Japan) of these tissue slices were used for infarct size analysis by digital planimetry.

Echocardiography was performed at baseline (BSL) and on 1, 3, 5, 7, 14, 21, 28 and 105 day(s) after the induction of MI (denoted as D1, D3, ..., and D105 hereafter) using a Vevo 770 high resolution ultrasound scanner (VisualSonics Inc., Toronto, Ontario, Canada). During each imaging session, anesthesia was induced with 2.5% isoflurane (inhaled with room air) and maintained with the minimum dose necessary to suppress the withdrawal reflex to foot pinch (1.0% to 1.4% isoflurane in air). Core body temperature was maintained at $37 \pm 0.5^\circ \text{C}$ with the aid of a heat lamp, a rectal thermocouple and a digital thermometer. The Vevo 770 was operated at 30 MHz center frequency, using an RMV707B transducer, producing an image resolution of $55 \mu\text{m}$ axially and $115 \mu\text{m}$ laterally at the fixed focal depth of 12.7 mm, which was positioned at the midventricular level of the mouse heart. Image sequences were acquired using the ECG-gated kilo hertz visualization (EKV) mode (Cherin et al. 2006) that retrospectively assembled image data over multiple cardiac cycles (2–3 min of acquisition time for short-axis view and 3–4 min for long-axis view) into one representative cardiac cycle composed of approximately 100 image frames. For 3-D analysis of the LV, five to six short-axis slices and three to four long-axis slices, with parallel acquisitions in each axis spaced 1 mm apart, were acquired encompassing the entire LV. A bi-axial, micrometer-adjustable motion stage integrated with the scanner was used to control

transducer positioning during acquisition (see Fig. 1). Detents offset by 90 degrees in the transducer clamp provided for the acquisition of perfectly orthogonal short- and long-axis image sequences. The imaging time per mouse was approximately 1 h, including the time for mouse preparation. Image artifacts were generally avoidable on BSL and 5 or more days after MI, however, they were present in D1 and D3 images, presumably as a direct result of surgery. These artifacts, observed during the subacute phase post-MI, made it necessary to exclude a limited number of datasets from the final analysis (exclusion rate = 37% on D1 and 10% on D3).

Volume quantification

Left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV) and ejection fraction (LVEF) were measured at regular intervals following MI. The volumes were calculated using Simpson's disc summation method and the long-axis image slices were used to determine the apical volumes when these were less clearly defined in the short-axis series. LVEF was calculated from LVEDV and LVESV.

Myocardial strain analysis

Myocardial radial strain (E_{rr}) was calculated in multiple two-dimensional (2-D) image planes encompassing the entire LV using an ultrasound speckle tracking method (Li et al. 2007). In brief, the LV was manually contoured on the end-diastolic frame of each image sequence. The LV region was then automatically populated with 2-D pixel blocks for tissue tracking. The size of the tracking pixel block was approximately 0.24×0.24 mm (a 16×16 pixel block containing 15×15 μ m pixels). Incremental displacement of myocardial tissue from one image frame to the next was estimated using the minimum sum of absolute differences (MSAD) criterion (Friemel et al. 1995). Parabolic interpolation, using the sum absolute difference (SAD) values corresponding to the minimum offset, and the two adjacent offsets, was then performed to determine displacement to subpixel resolution. After each frame-to-frame displacement estimation, the center of the pixel block was updated (to integer pixel resolution) so as to track the displacement of an approximately common tissue subregion through the cardiac cycle.

For regional strain analysis, standard methods (Cerqueira et al. 2002) were used to segment each slice of the LV into six sectors (in both short-axis and long-axis views). Segmental radial strain was calculated as the mean over each sector. To achieve higher spatial resolution, each of the six sectors was further divided into six subsectors yielding a total of 36 subsectors per slice. In each subsector, the peak E_{rr} was measured as the maximum positive E_{rr} over the complete cardiac cycle (not necessarily at ES). Regional E_{rr} calculated from multiple short-axis slices was color mapped to the underlying 3-D LV surface using a Hammer projection (Hunter and Smail 1988).

Segmentation of the LV into infarct, adjacent and remote zones

We have previously reported that regional myocardial contractile function in mice can vary significantly based on position relative to the infarct (Epstein et al. 2002; Young et al. 2006). Therefore, in addition to the standard sector segmentation, the 3-D LV was also classified into three physiologically-distinct zones: infarct, adjacent and remote zones. Regional peak E_{rr} normalized by the corresponding baseline value was used to differentiate infarcted from noninfarcted myocardium. To identify the optimal threshold for normalized peak E_{rr} , receiver operating characteristic (ROC) analysis was performed using histologic infarct size as determined by *post mortem* tissue staining with TTC. Photographs of short-axis tissue slices were divided circumferentially into 36 sectors (corresponding to the 36-subsector segmentation in ultrasound analysis) and sectors that contained infarct that extended greater than 1/2 of that arc length were classified as infarct, otherwise they were classified as

noninfarct. The circumferential extent of infarction was defined as the percentage of the midwall LV circumference that subtended infarcted tissue, as described previously (Pfeffer et al. 1979). The overall extent of infarction in the 3-D LV myocardium was calculated as slice-area-weighted sum of the infarct size in individual slices. Values of normalized peak E_{Tr} from 0% to 100%, at 2% increments, were compared with histologic infarct size to determine the optimal threshold for detecting infarcted myocardium. The classification sensitivity and specificity for each value was assessed by ROC analysis and the value that yielded the largest sum of sensitivity and specificity was chosen as the optimal threshold.

To prepare the echo-derived E_{Tr} data for ROC analysis, the peak E_{Tr} maps for the short-axis slices were unfolded from the center of the septum, and were stacked from apex to base according to the 3-D LV geometry. To ensure that each infarct zone was spatially continuous, a region growing method was applied that started from a “seed” region on the 3-D E_{Tr} map with the lowest normalized peak E_{Tr} value and grew outward from the seed until the predefined threshold was met. A second border was then generated 1.0 mm outside of the infarct border to define the adjacent zone. The two initial border-lines were then smoothed by a three sample moving average filter. All remaining regions beyond the infarct and adjacent zones were defined as remote zones. This segmentation process was repeated for each mouse heart at each time point after MI.

LV dyssynchrony analysis

The time to peak E_{Tr} (T_{peak}) with respect to the ECG R-wave was calculated for dyssynchrony analysis, consistent with the previous dyssynchrony studies (Leitman et al. 2004; Suffoletto et al. 2006; Mollema et al. 2007). The T_{peak} was obtained using a previously described method (Li et al. 2008) for the 3-D LV myocardium, in both the standard sectors and the three distinct zones as defined by the ROC-informed infarct analysis. The standard deviation of T_{peak} ($SD_{T_{peak}}$) was calculated for each of the three zones and for the entire LV myocardium to quantify the degree of regional dyssynchrony. The evolution of regional dyssynchrony was assessed by performing serial $SD_{T_{peak}}$ analysis at regular intervals over time following MI.

To quantify the dyssynchronous systolic bulging (dyskinesia) associated with acute and subacute MI, a novel metric, contraction index (CI), was defined to describe the ratio of productive radial displacement to the total radial displacement, such that a low CI indicates greater paradoxical wall thinning during systole. Mathematically, the ratio of the sum of signed radial displacements (accounting for differential polarity of displacements) to the sum of unsigned radial displacements (disregarding the polarity of displacements) was first calculated for each segment in a slice at each time point in the cardiac cycle as follows:

$$eff(t_j) = \frac{\sum_i d(i, t_j)}{\sum_i |d(i, t_j)|} w(t_j) \quad (1)$$

where d is the mean radial displacement of tracked blocks within segment i at time point t_j , eff is the calculated efficiency at that time point, and w is a weighting factor derived from the signed sum.

$$w(t_j) = \frac{N \sum_i |d(i, t_j)|}{\sum_j \sum_i |d(i, t_j)|} \quad (2)$$

CI was defined as the area under the curve of the efficiency - $eff(t_j)$ – for all segments in a slice over the complete cardiac cycle.

$$CI = \int_{t_0}^{t_N} eff(t_j) dt \quad (3)$$

CI is thus the integral, with respect to time, of a weighted ratio of the sum of signed radial displacements to the sum of unsigned radial displacements. A ratio of unity represents completely uniform radial displacement, whereas a ratio approaching zero indicates the degree of anti-phase radial displacement such as that encountered during paradoxical wall thinning (systolic dyskinesia). At each time point following MI in this study, CI was calculated from the regional radial displacement values for each of the 36 subsectors located in the single most midventricular short-axis slice of the LV.

These data were compared with four of the most prevalent dyssynchrony metrics to evaluate the utility of the CI. The velocity vector index (VVI) (Yu et al. 2002; Vannan et al. 2005) was evaluated by computing the maximum difference between the time to peak velocity of each of the 36 subsectors of the midventricular myocardium. Temporal uniformity of strain (Leclercq et al. 2002) was computed by plotting E_{rr} at each of the 36 subsectors versus spatial position of the sector. Fourier analysis was used to determine the ratio of the zero to the first-order power terms, indicating the uniformity strain throughout the myocardium. The activation delay vector (ADV) (Wyman et al. 2002) was computed by multiplying unit vectors at each of the 36 subsectors by E_{rr} of that subsector. These vectors were summed to determine the principal strain vector and the area under the curve of the magnitude of the vector was used to give an estimate of dyssynchrony. SD_T_{peak} was computed as described above. Data for each metric were normalized to the maxima of that metric. VVI, ADV and SD_T_{peak} data were inverted to facilitate direct comparison between the metrics (*i.e.*, smaller metric value corresponded with greater dyssynchrony).

Statistical analysis

All data are presented as mean $\pm$ 1 SD. One-way analysis of variance (ANOVA) was used to test for the differences in peak E_{rr} between the infarct, adjacent and remote zones, and the differences of T_{peak} in these zones. The infarct size in each ultrasound image slice acquired *in vivo* was compared to the corresponding histologic slice, and the agreement was determined using linear regression and Bland-Altman analysis (Bland and Altman 1986). A value of $p < 0.05$ was considered significant.

RESULTS

LV remodeling after MI

All eight mice survived the study and were all used in the final analysis. As the mice employed in this study were matched for age, sex and genotype; baseline values for LV chamber size and wall thickness were consistent between mice with acceptably small standard errors. After MI, all mice exhibited various degrees of LV dilation and wall thinning. The LVEDV, LVESV and LVEF were serially quantified following MI, as graphed in Figure 2.

Segmentation of infarct, adjacent and remote zone using regional peak E_{rr}

Myocardial tissue staining with TTC was performed *post mortem* to provide a histologic gold standard for *in vivo* infarct size determination. The infarct zone was clearly delineated in seven hearts but one mouse heart was excluded due to a technical failure in the TTC staining procedure. For *in vivo* segmentation of the infarct zone, ROC analysis was

performed to identify the optimal threshold using the regional peak E_{Tr} measured on D105 (normalized to the baseline value). At the threshold of 32% of normalized peak E_{Tr} , the ROC analysis indicated a sensitivity of 83%, a specificity of 84% and an area under the curve (AUC) of 0.90.

Ultrasound and histologic measurements of infarct size were compared slice by slice for each of $N = 7$ mouse hearts, as shown in Figure 3A. The top row displays regional peak E_{Tr} maps on five short-axis ultrasound image slices, with red or orange colors indicating the infarct zone. The bottom row contains the photographs of five TTC-stained tissue slices from the same mouse heart, with infarct regions in white and viable regions in red. The percent infarct size in the second slice is illustrated in both the ultrasound image and the tissue photograph. The large red arrows indicate thinning of the anterior wall in the midventricular and apical aspects of the heart. The agreement between the ultrasound and histologic measurements of infarct size was tested using linear regression (Fig. 3B) and Bland-Altman analysis (Fig. 3C) (Bland and Altman 1986). A strong correlation of $R = 0.89$ was found between the two measurements, with $p < 0.01$.

Regional peak E_{Tr} calculated from multiple short-axis slices was color mapped to the underlying 3-D LV by Hammer projection (Hunter and Smaill 1988), as shown in Figure 4. The infarct, adjacent and remote zones are delineated on the D1 map. The infarct, adjacent and remote zones at this time represented $30 \pm 13\%$, $25 \pm 9\%$ and $45 \pm 10\%$ of the LV muscle mass, respectively. The BSL map demonstrated relatively uniform E_{Tr} over the entire LV. However, when assessed on D1 after MI, E_{Tr} in the anterior and anterolateral walls near the apex (infarct zone) had abruptly declined, reflecting the immediate impact of MI on contractile function.

Serial analysis of E_{Tr} and T_{peak} in the infarct, adjacent and remote zones

The evolution of regional E_{Tr} following MI was analyzed in the infarct, adjacent and remote zones, as well as in the standard six sectors per slice. Example serial analyses of cardiac strain are illustrated in Figures 5 and 6, in the short-axis and long-axis views, respectively. In these graphs, global E_{Tr} function was reported by averaging E_{Tr} in all myocardial areas over the 3-D LV. Compared with BSL, on D1 after MI, E_{Tr} was dramatically reduced ($>80\%$ decrease) in the infarct zone. E_{Tr} was also reduced by 30%–50% in the adjacent zone but was relatively well-preserved in the remote zone. Considerable delays in T_{peak} were observed in the adjacent and infarct zones at every time point post-MI.

Evolution of LV dyssynchrony following MI

Regional peak E_{Tr} in the three physiologically-distinct zones, as well as global peak E_{Tr} over the entire LV, was serially assessed at baseline (BSL) and over time following MI as shown in Figure 7A. At BSL, E_{Tr} was relatively uniform throughout the LV, with a peak value of 0.36 ± 0.04 . Remote zone E_{Tr} was relatively well-preserved on D1 but gradually declined to approximately 70% of the BSL level by D28 post-MI. In the adjacent zone, a dramatic decrease in E_{Tr} (to approximately 38% of the BSL value) was measured on D1. A trend toward recovery was observed in adjacent zone E_{Tr} from D1 to D7, followed by a gradual decline that again approached 38% of its baseline value by D28 post-MI. In the infarct zone, E_{Tr} declined precipitously on D1 and remained suppressed at about 15% of its baseline value throughout the study. The global E_{Tr} , calculated without regard for the three zones, exhibited an abrupt decline on D1 followed by a trend toward gradual decline thereafter, consistent with the trend exhibited by LVEF, Figure 2B. One-way analysis of variance (ANOVA) of E_{Tr} in the three zones indicated that the differences between the three zones were statistically significant ($p < 0.05$) at every time point other than baseline.

The time course of SD_T_{peak} following MI was analyzed as shown in Figure 7B. At BSL, the SD_T_{peak} was low for the entire LV. On D1, SD_T_{peak} in the infarct zone sharply increased to nearly twice its BSL value and reached a steady plateau that was largely maintained out to D28. SD_T_{peak} in the remote zone exhibited a significant increase on D1 that gradually continued with the progression of LV remodeling. The adjacent zone exhibited behavior similar to the infarct zone, with a sharp increase in SD_T_{peak} on D1 that was maintained out to D28 post-MI. For the entire LV, the global SD_T_{peak} rapidly increased to over twice its BSL value to reach a plateau that declined only slightly by D28 post-MI.

LV dyssynchrony early after MI

The contraction index (CI) was derived from the sum of signed radial displacements and the sum of unsigned radial displacements, as illustrated in Figure 8. Panels 8A and C illustrate the CI principle in a normal mouse at BSL, while panels 8B and D illustrate CI in a mouse assessed early after MI. The CI, as well as four established dyssynchrony metrics – activation delay vector (Wyman et al. 2002) (ADV), velocity vector index (Yu et al. 2002; Vannan et al. 2005) (VVI), temporal uniformity of strain (Leclercq et al. 2002) (TUS) and standard deviation of time to peak radial strain (Suffoletto et al. 2006) (SDT) – were computed for midventricular, short-axis slices for each mouse at each time point in the serial study (see Fig. 9). The time course of the CI curve exhibited a significant decrease at D1 that continued a steep decline until D3, after which it rapidly improved to reach steady-state by D14. In contrast, the ADV, VVI, TUS and SDT metrics all exhibited a significant decline on D1, then reached steady-state values between D7 and D14 that either remained steady (VVI) or improved by varying degrees (ADV, TUS and SDT) by D28.

It has been demonstrated that LV dyssynchrony immediately after MI (as measured by maximal difference of T_{peak} [MD_T_{peak}]) predicts LV remodeling late after MI (Mollema et al. 2007). To assess the predictive power of our newly-developed metric of cardiac dyssynchrony (CI), we used our strain measurements from D1 post-MI to calculate three other dyssynchrony metrics: T_{peak} in the infarct zone, standard deviation of T_{peak} (SD_T_{peak}) and maximal difference of T_{peak} (MD_T_{peak}) measured over the entire LV for consistency with (Mollema et al. 2007). We then compared these metrics with D1 CI for their ability to predict the increase in LVESV ($\Delta LVESV$) that occurred between BSL and D105 post-MI. Table 1 lists the R values resulting from linear regression between each of the D1 dyssynchrony metrics and $\Delta LVESV$ on D105, as well as the p values and percent prediction errors. In this analysis, the newly-developed contraction index (CI) yielded the strongest correlation, the lowest p value and smallest prediction error among the metrics examined in this comparison.

Remote dyssynchrony develops in concert with LV remodeling

Regional LV dyssynchrony analysis revealed very similar trends in the progression of remote zone dyssynchrony and LV remodeling following MI. The comparison between remote zone SD_T_{peak} and LVESV indicated that the gradual increase in remote zone SD_T_{peak} strongly correlated with the increase in LVESV, and a linear regression analysis demonstrated a strong agreement ($R = 0.70$, $p < 0.05$) between these two parameters, as shown in Figure 10.

DISCUSSION AND SUMMARY

Both cardiac MRI and echocardiography have previously been used to serially assess the changes in 3-D LV structure and function that result from MI in mice (Ross et al. 2002; Young et al. 2006). However, this study provides the first serial, 3-D analysis of mechanical

LV dyssynchrony in mice after MI. The superior temporal resolution of echocardiography over cardiac MRI played an essential role in making it possible to apply intramural speckle-tracking methods to the serially-acquired datasets (Korinek et al. 2005; Li et al. 2008). In the current study, speckle-tracking was able to differentiate between the three distinct LV dyssynchrony patterns characteristic of infarct, adjacent and remote myocardium, both early and late after reperfused MI. While the conventional dyssynchrony metric of SD_T_{peak} sufficed to characterize the progressive onset of dyssynchrony that occurs in the LV late after MI, neither it nor three other dyssynchrony metrics adequately differentiated between late dyssynchrony and the systolic dyskinesia (paradoxical wall thinning) that afflicts the compliant infarct zone early after MI. A new metric, contraction index, was therefore developed to directly measure the ratio of productive radial displacement (signed sum) to total radial displacement (unsigned sum) over the cardiac cycle on a segmental basis. A direct comparison of this focused metric (CI) to three other previous metrics revealed that CI (as determined on D1 post-MI) was the strongest predictor for the long-term increase in LVESV initiated by reperfused MI. This is probably due to the fact that CI is the only one of the tested metrics that takes the polarity of systolic radial displacement into account, whereas the other tested metrics use only timing information. Thus, CI may find utility in predicting the late outcome of MI in patient populations, as shown previously for global MD_T_{peak} by (Mollema et al. 2007). Finally, careful comparison of the various dyssynchrony metrics to the time course of global LV remodeling (as measured by serial assessment of LVESV) revealed, for the first time, that remote zone LV dyssynchrony (as measured by SD_T_{peak}) develops in concert with global LV remodeling. This finding has important implications, because it suggests that the mechanism(s) underlying remote zone LV dyssynchrony have strong mechanical component(s) (Cheng et al. 2009a,b).

In the current study, regional LV radial strain E_{rr} was calculated both by conventional sector analysis and according to the three physiologically distinct regions of interest in the LV after MI (infarct, adjacent and remote myocardium). In both cases, the radial strain analyses were performed over the entire extent of the 3-D LV by summing the contributions of the 2-D E_{rr} measurements from complete stacks of contiguous 2-D short-axis slices. The 3-D LV myocardium was segmented into infarct, adjacent and remote zones according to regional peak E_{rr} . ROC curve analysis of the *in vivo* peak E_{rr} based segmentation of the infarct zone yielded a sensitivity of 83% and a specificity of 84% compared with the standard *postmortem* histologic determination. A slice-by-slice comparison of the infarct zone segmented *in vivo* and *postmortem* revealed a strong correlation with $R = 0.89$. Regional E_{rr} of the entire 3-D LV was color mapped to the underlying LV anatomy using a Hammer projection, providing for a more comprehensive method for visualizing LV functional changes following MI than the conventional 2-D bullseye plot.

The limitations of this study are worthy of discussion. The current study focused on the mechanical aspects of LV dyssynchrony and failed to address electrical dyssynchrony by ECG analysis. Nevertheless, follow up studies conducted in a parallel set of post-MI mice detected a significant 36% increase in the QRS/RR ratio between baseline and D14 post-MI. Infarct size in this study was determined by indirect means using ROC analysis of regional E_{rr} at D105 compared with histologic infarct size determined at the same timepoint. The segmentation of the LV myocardium into infarct, adjacent and remote zones at earlier timepoints therefore assumes that this relationship remains constant over time. It would clearly have been preferable to perform similar ROC analyses at every timepoint, but this strategy would have required tissue harvest at every timepoint and would not have been compatible with the serial study performed by echocardiography. Also, since infarct size was determined by indirect means, we did not attempt to correlate infarct size with the degree of LV remodeling or dyssynchrony. This point notwithstanding, the relationship between infarct size and subsequent LV remodeling is now well established (Watzinger et

al. 2002; Lund et al. 2007). Another limitation lies in the fact that the 3-D ultrasound data were reconstructed from 2-D short-axis image slices sampled at 1-mm intervals and, thus, the 3-D Hammer projections involved some degree of interpolation rather than reflecting true 3-D volumetric data. A truly 3-D ultrasound acquisition of volumetric data acquired by 2-D arrays would provide opportunities to make measurements of true 3-D displacement vectors and strain tensors, which would further expedite investigation of 3-D cardiac mechanics and the underlying pathophysiology of MI. Although high-frequency 2-D arrays for mouse cardiac imaging may not be readily available in the near future due to considerable technical challenges, finely sampled 2-D image slices that are precisely registered in both time and space with advanced mathematical modeling using additional cardiac mechanical and electrophysiological boundary conditions, may provide solutions for studying the true 3-D dynamics of intramyocardial strain.

Despite these limitations, this study's finding that post-infarct LV remodeling develops in concert with mechanical LV dyssynchrony may prove useful in animal studies aimed at elucidating the molecular mechanisms underlying this important phenomenon. In particular, future studies conducted in genetically-manipulated mice should be informative in further defining the relationship between LV remodeling and LV dyssynchrony at the molecular level. The resulting understanding could ultimately lead to the development of novel therapies for the treatment and/or prevention of post-infarct LV dyssynchrony. Also with regard to clinical translation, Table 1 suggests that the newly developed contraction index (CI) may ultimately prove to be a stronger predictor of subsequent LV remodeling than many of the dyssynchrony metrics that have widely been employed to date.

Acknowledgments

This work was supported by a NIH grants EB001826, RR022582 (to JAH), and R01HL058582 (to BAF). Dr. French is a Fellow of the American Heart Association. The authors wish to thank Dr. Reid H. Harris and Daniel M. O'Connor for their technical contributions.

REFERENCES

- Akaishi M, Weintraub WS, Schneider RM, Klein LW, Agarwal JB, Helfant RH. Analysis of systolic bulging. Mechanical characteristics of acutely ischemic myocardium in the conscious dog. *Circ Res*. 1986; 58:207–217.
- Bader H, Garrigue S, Lafitte S, Reuter S, Jais P, Haissaguerre M, Bonnet J, Clementy J, Roudaut R. Intra-left ventricular electromechanical asynchrony: A new independent predictor of severe cardiac events in heart failure patients. *J Am Coll Cardiol*. 2004; 43:248–256. [PubMed: 14736445]
- Bax JJ, Gorgalsan J III. Echocardiography and noninvasive imaging in cardiac resynchronization therapy: Results of the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) study in perspective. *J Am Coll Cardiol*. 2009; 53:1933–1943. [PubMed: 19460606]
- Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986; 1:307–310. [PubMed: 2868172]
- Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002; 105:539–542. [PubMed: 11815441]
- Chang S-A, Chang H-J, Choi SI, Chun EJ, Yoon YE, Kim H-K, Kim Y-J, Choi D-J, Sohn D-W, Helm RH, Lardo AC. Usefulness of left ventricular dyssynchrony after acute myocardial infarction, assessed by a tagging magnetic resonance image derived metric, as a determinant of ventricular remodeling. *Am J Cardiol*. 2009a; 104:19–23. [PubMed: 19576315]
- Cheng A, Helm RH, Abraham TP. Pathophysiological mechanisms underlying ventricular dyssynchrony. *Europace*. 2009b; 11:v10–v4. [PubMed: 19861385]

- Cherin E, Williams R, Needles A, Liu G, White C, Brown AS, Zhou Y, Foster FS. Ultrahigh frame rate retrospective ultrasound microimaging and blood flow visualization in mice *in vivo*. *Ultrasound Med Biol*. 2006; 32:683–691. [PubMed: 16677928]
- Cho G-Y, Kim H-K, Kim Y-J, Choi D-J, Sohn D-W, Oh B-H, Park Y-B. Electrical and mechanical dyssynchrony for prediction of cardiac events in patients with systolic heart failure. *Heart*. 2010; 96:1029–1032. [PubMed: 19910289]
- Cho G-Y, Song J-K, Park W-J, Han S-W, Choi S-H, Doo Y-C, Oh D-J, Lee Y. Mechanical dyssynchrony assessed by tissue Doppler imaging is a powerful predictor of mortality in congestive heart failure with normal QRS duration. *J Am Coll Cardiol*. 2005; 46:2237–2243. [PubMed: 16360052]
- Delgado V, Ypenburg C, van Bommel RJ, Tops LF, Mollema SA, Marsan NA, Bleeker GB, Schalij MJ, Bax JJ. Assessment of left ventricular dyssynchrony by speckle tracking strain imaging: Comparison between longitudinal, circumferential, and radial strain in cardiac resynchronization therapy. *J Am Coll Cardiol*. 2008; 51:1944–1952. [PubMed: 18482662]
- Epstein FH, Yang Z, Gilson WD, Berr SS, Kramer CM, French BA. MR tagging early after myocardial infarction in mice demonstrates contractile dysfunction in adjacent and remote zones. *Magn Reson Med*. 2002; 48:399–403. [PubMed: 12210951]
- French BA, Kramer CM. Mechanisms of post infarct left ventricular remodeling. *Drug Discov Today Dis Mech Cardiovasc Dis*. 2007; 4:185–196.
- Friemel BH, Bohs LN, Trahey GE. Relative performance of two-dimensional speckle-tracking techniques: Normalized correlation, non-normalized correlation and sum-absolute-difference. *Ultrason Symp IEEE Proc*. 1995; 2:1481–1484.
- Hunter PJ, Smaill B.H. The analysis of cardiac function: A continuum approach. *Prog Biophys Mol Biol*. 1988; 52:101–164. [PubMed: 3076684]
- Jackson BM, Gorman JH, Moainie SL, Guy TS, Narula N, Narula J, St. John-Sutton MG, Edmunds LH, Gorman RC. Extension of border-zone myocardium in postinfarction dilated cardiomyopathy. *J Am Coll Cardiol*. 2002; 40:1160–1167. [PubMed: 12354444]
- Korinek J, Wang J, Sengupta PP, Miyazaki C, Kjaergaard J, McMahon E, Abraham TP, Belohlavek M. Two-dimensional strain - A Doppler-independent ultrasound method for quantitation of regional deformation: Validation *in vitro* and *in vivo*. *J Am Soc Echocardiogr*. 2005; 18:1247–1253. [PubMed: 16376750]
- Leclercq C, Faris O, Tunin R, Johnson J, Kato R, Evans F, Spinelli J, Halperin H, McVeigh E, Kass D. Systolic improvement and mechanical resynchronization does not require electrical synchrony in the dilated failing heart with left bundle-branch block. *Circulation*. 2002; 106:1760–1763. [PubMed: 12356626]
- Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, Kaluski E, Krakover R, Vered Z. Two-dimensional strain—A novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr*. 2004; 17:1021–1029. [PubMed: 15452466]
- Li Y, Garson CD, Xu Y, Beyers RJ, Epstein FH, French BA, Hossack JA. Quantification and MRI validation of regional contractile dysfunction in mice post myocardial infarction using high resolution ultrasound. *Ultrasound Med Biol*. 2007; 33:894–904. [PubMed: 17434660]
- Li Y, Garson CD, Xu Y, French BA, Hossack JA. Assessing cardiac dyssynchrony in mice post myocardial infarction using speckle tracking of high frequency ultrasound images. *Ultrasound Med Biol*. 2008; 34:1063–1075. [PubMed: 18313202]
- Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Stafford R, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J, on behalf of the American Heart Association Statistics Committee and Stroke Statistics S. Heart Disease and Stroke Statistics—2010 Update: A Report From the American Heart Association. *Circulation*. 2010; 121:e46–e215. [PubMed: 20019324]
- Lund GK, Stork A, Muellerleile K, Barmeyer AA, Bansmann MP, Knäfel M, Schlichting U, Müller M, Verde PE, Adam G, Meinertz T, Saeed M. Prediction of left ventricular remodeling and

- analysis of infarct resorption in patients with reperfused myocardial infarcts by using contrast-enhanced MR imaging. *Radiology*. 2007; 245:95–102. [PubMed: 17885184]
- Mann DL. Mechanisms and models in heart failure. *Circulation*. 1999; 100:999–1008. [PubMed: 10468532]
- Mann DL, Bristow MR. Mechanisms and models in heart failure: The biomechanical model and beyond. *Circulation*. 2005; 111:2837–2849. [PubMed: 15927992]
- Mollema SA, Liem SS, Suffoletto MS, Bleeker GB, van der Hoeven BL, van de Veire NR, Boersma E, Holman ER, van der Wall EE, Schalij MJ, Gorcsan J III, Bax JJ. Left ventricular dyssynchrony acutely after myocardial infarction predicts left ventricular remodeling. *J Am Coll Cardiol*. 2007; 50:1532–1540. [PubMed: 17936151]
- Noma S, Askenase AD, Agarwal JB, Helfant RH. The effect of changes in after load on systolic bulging. *Circulation*. 1988; 77:221–226. [PubMed: 3335069]
- Pfeffer M, Pfeffer J, Fishbein M, Fletcher P, Spadaro J, Kloner R, Braunwald E. Myocardial infarct size and ventricular function in rats. *Circ Res*. 1979; 44:503–512. [PubMed: 428047]
- Porciani MC, Cappelli F, Perrotta L, Chiostrì M, Rao CM, Pieragnoli P, Ricciardi G, Michelucci A, Jelic S, Padeletti L. Has mechanical dyssynchrony still a role in predicting cardiac resynchronization therapy response? *Echocardiography*. 2010; 27:831–838. [PubMed: 20642457]
- Ross AJ, Yang Z, Berr S, Gilson W, Petersen W, Oshinski J, French B. Serial MRI evaluation of cardiac structure and function in mice after reperfused myocardial infarction. *Magn Reson Med*. 2002; 47:1158–1168. [PubMed: 12111962]
- Shin S-H, Hung C-L, Uno H, Hassanein AH, Verma A, Bourgoun M, Kober L, Ghali JK, Velazquez EJ, Califf RM, Pfeffer MA, Solomon SD, for the Valsartan in Acute Myocardial Infarction Trial I. Mechanical dyssynchrony after myocardial infarction in patients with left ventricular dysfunction, heart failure, or both. *Circulation*. 2010; 121:1096–1103. [PubMed: 20176989]
- Strickberger SA, Conti J, Daoud EG, Havranek E, Mehra MR, Pina IL, Young J, American College of Cardiology Foundation and the Heart Failure Society of America. Patient selection for cardiac resynchronization therapy: From the Council on Clinical Cardiology Subcommittee on Electrocardiography and Arrhythmias and the Quality of Care and Outcomes Research Interdisciplinary Working Group, in collaboration with the Heart Rhythm Society. *Circulation*. 2005; 111:2146–2150. Endorsed by the. [PubMed: 15851622]
- Suffoletto M, Dohi K, Cannesson M, Saba S, Gorcsan J III. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. *Circulation*. 2006; 113:960–968. [PubMed: 16476850]
- Sutton M, Sharpe N. Left ventricular remodeling after myocardial infarction: Pathophysiology and therapy. *Circulation*. 2000; 101:2981–2988. [PubMed: 10869273]
- Vannan M, Pedrizzetti G, Li P, Gurudevan S, Houle H, Main J, Jackson J, Nanda N. Effect of cardiac resynchronization therapy on longitudinal and circumferential left ventricular mechanics by velocity vector imaging: Description and initial clinical application of a novel method using high-frame rate B-mode echocardiographic images. *Echocardiography*. 2005; 22:826–830. [PubMed: 16343165]
- Watzinger N, Lund GK, Higgins CB, Wendland MF, Weinmann H-J, Saeed M. The potential of contrast-enhanced magnetic resonance imaging for predicting left ventricular remodeling. *J Magn Reson Imaging*. 2002; 16:633–640. [PubMed: 12451576]
- Wyman BT, Hunter W, Prinzen F, Faris O, McVeigh E. Effects of single- and biventricular pacing on temporal and spatial dynamics of ventricular contraction. *Am J Physiol Heart Circ Physiol*. 2002; 282:H372–H379. [PubMed: 11748084]
- Yang Z, Bove CM, French BA, Epstein FH, Berr SS, DiMaria JM, Gibson JJ, Carey RM, Kramer CM. Angiotensin II type 2 receptor overexpression preserves left ventricular function after myocardial infarction. *Circulation*. 2002; 106:106–111. [PubMed: 12093778]
- Young AA, French BA, Yang Z, Cowan BR, Gilson WD, Berr SS, Kramer CM, Epstein FH. Reperfused myocardial infarction in mice: 3-D mapping of late gadolinium enhancement and strain. *J Cardiovasc Magn Reson*. 2006; 8:685–692. [PubMed: 16891227]
- Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, Lin H, Kong SL, Lam YM, Hill MR, Lau CP. Tissue Doppler echocardiographic evidence of reverse remodeling and improved

synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation*. 2002; 105:438–445. [PubMed: 11815425]

Fig. 1.

Photograph illustrating the motion stage and adjustable transducer mount available with the Vevo 770 (VisualSonics, Inc.). The bi-axial, micrometer-adjustable motion stage at bottom was used to reposition the mouse beneath the transducer to acquire a contiguous stack of short-axis images sequences at 1 mm intervals covering the entire heart from base to apex. Detents offset by 90 degrees in the transducer clamp provided for the acquisition of perfectly orthogonal short- and long-axis image sequences.

Fig. 2. The time course of left ventricular end diastolic and end systolic volumes (LVEDV and LVESV, respectively) (A) and ejection fraction (LVEF) (B) following myocardial infarction. (N = 5 for day 1 and N = 8 for all other time points).

Fig. 3. (A) Measurement of percent infarct size by ultrasound *in vivo* (top) and by histologic tissue staining (bottom). (B) Slice-by-slice correlation of percent infarct size (IS) measured by ultrasound (US) and histologic tissue staining. (C) Bland-Altman plot indicates the mean differences with the solid lines and the 95% confidence intervals (calculated as mean $\pm$ 2 standard deviations) with the dashed lines. In both graphs, a different color/shaped marker is used for each mouse heart ($N = 7$) and four to six slices were assessed from each mouse heart.

Fig. 4.

Regional peak E_{TT} mapped to Hammer projection of 3-D left ventricle. Panels A to D summarize the regional peak E_{TT} results for a single mouse at baseline (A), day 1 (B), day 7 (C) and day 28 (D). The fine black line on the D1 Hammer map indicates the infarct zone (as defined by ROC analysis), while the fine red line delineates the border between the adjacent and remote zones. A = anterior; AL = anterolateral; AS = anterior septal; P = posterior; PL = posterolateral; PS = posterior septal.

Fig. 5.

Regional radial strain analysis in the midventricular short-axis view at baseline, and on day 1, day 7 and day 28. Left column: myocardial displacement maps, color-coded according to the displacement magnitude. The infarct zone in the day 1 image is outlined in red and the adjacent zone is outlined in orange. Middle column: E_{rr} (radial strain) vs. time curves for the standard six sectors. The time points on the x-axis depict a single, representative cardiac cycle as compiled by the retrospective EKV capability on the Vevo 770 (VisualSonics, Inc.). Right column: E_{rr} vs. time curves for the infarct, adjacent and remote zones. Rem = remote zone; Adj = adjacent zone; Inf = infarct zone; All = all LV regions.

Fig. 6.

Regional radial strain analysis in the midventricular long-axis view at baseline, and on day 1, day 7 and day 28. Similar format as in Figure 5. B = basal; m= midventricular; a = apex; Ant = anterior; Pst = posterior.

Fig. 7.

(A) Time course of peak E_{rr} (radial strain) in the remote, adjacent and infarct zones, and for the entire left ventricle. Significant differences were found between the three different physiological regions ($*p < 0.05$). (B) Time course of standard deviation of time to peak radial strain following infarction in the three zones and for the entire LV ($N = 5$ for day 1 and $N = 8$ for all other time points).

Fig. 8.

Illustration of contraction index (CI). In (A) and (C): S1, S2 and S3 represent segmental radial displacements (three segments are illustrated here for simplicity, 36 were used in the study). The green solid lines are the aggregate sums of signed radial displacements S1, S2 and S3; while the green dotted lines are the sums of the unsigned, absolute values of radial displacements. Panel (A) illustrates the principle in a normal mouse at baseline, where all segments are free of negative values and the green dotted line is therefore coincident with the green solid line. Panel (B) illustrates a post-MI mouse with a dyskinetic segment represented by a red line (S2). Plots of the weighted ratios of the sum of signed displacements to the sum of unsigned displacements for panels (A) and (B) are shown in panels (C) and (D), respectively.

Fig. 9.

Time course of four established dyssynchrony metrics in comparison to Contraction Index (CI) in the mouse heart after MI. Shown here are the activation delay vector (ADV), velocity vector index (VVI), temporal uniformity of strain (TUS), standard deviation of time to peak strain (SDTP) and the newly-developed metric: contraction index (CI) as calculated for $N = 5$ mice for D1 and $N = 8$ for all other time points. ADV, VVI, and SDT data have been inverted to facilitate direct comparison between the five metrics (*i.e.*, such that larger metric values reflect more synchronous contraction).

Fig. 10.

LV dyssynchrony in the remote zone develops in concert with LV remodeling: (A) Left ventricular end systolic volume (LVESV) and remote zone standard deviation of time to peak radial strain (SD_T_{peak}) over time after infarction. (B) Linear regression of LVESV and remote zone SD_T_{peak} (N = 5 for D1 and N = 8 for all other time points). In both graphs, a different color/shaped marker is used for each mouse heart (N = 8) and each mouse heart was assessed at seven to eight time points.

Table 1D1 LV dyssynchrony predicts Δ LVESV on D105 (N = 5)

	R	p value	Prediction error (%)
Infarct T_{peak}^* vs. Δ LVESV [†]	0.71	0.104	17.1
LV SD- $T_{\text{peak}}^{\ddagger}$ vs. Δ LVESV	0.79	0.089	-13.7
LV MD- $T_{\text{peak}}^{\S}$ vs. Δ LVESV	0.87	0.072	10.4
CI [¶] vs. Δ LVESV	0.93	0.0042	-2.62

LV = left ventricular; LVESV = left ventricular end-systolic volume; T_{peak} = time to peak radial strain; SD = standard deviation; MD = maximal difference; CI = contraction index.