Imaging of Murine Infarcts Using Myocardial Elastography at Both High Temporal and Spatial Resolution

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Abstract—Myocardial elastography is a novel method for noninvasively assessing regional myocardial function, with the advantages of high spatial and temporal resolution, and high precision. In this paper, in vivo experiments were performed in anesthetized normal and infarcted mice (one day post-LAD ligation) using a high-resolution (30 MHz) ultrasound system (Vevo 770 VisualSonics Inc.). Radio-frequency (RF) signals of the left ventricle (LV) in long-axis view and the associated electrocardiogram (ECG) were simultaneously acquired. Using the retrospective ECG gating technique, an extremely high frame rate (up to 8 kHz) was achieved that resulted in high-quality incremental displacement and strain estimation of the myocardium. The incremental results were further accumulated to obtain the cumulative displacements and strains. Results clearly depicted the contraction, relaxation, thickening and thinning of LV in both normal and infarcted mice, and also evidently indicated reduced motion and deformation in the infarcted myocardium. The elastograms indicated that the infarcted regions underwent thinning during systole, rather than thickening as in the normal case. Preliminary statistical results from nine normal mice and seven infarcted mice indicated the capability of the cumulative strain in differentiating infarcted from normal myocardium. In conclusion, myocardial elastography could provide regional strain information at a high frame rate (8 kHz) with high resolution and long examination time.

Elastography [4] has been shown successful in estimating and imaging the local strains in tissues undergoing external, quasi-static compression. Myocardial elastography is a novel technique for non-invasively imaging regional myocardial function [5]. It utilizes the inherent cardiac muscle function as the mechanical stimulus and acquires consecutive radio-frequency (RF) signals to estimate the axial displacements and strains of the myocardium during a cardiac cycle. A preliminary clinical study in a patient showed the infarcted regions could be identified and differentiated from non-infarcted ones using envelope-detected signals [6]. Another clinical study on seven normal human subjects also indicated that myocardial elastography could offer comparable quality estimates to those obtained with MR cardiac tagging, with the added advantages of higher temporal and spatial resolution [7].

High-frequency ultrasound systems have recently become commercially available. Pernot et al. developed a high frame-rate data acquisition system based on a high-frequency Vevo 770 system (VisualSonics Inc., Toronto, ON, Canada) and the retrospective ECG gating technique [8]. In this paper, the same system was used to acquire the RF signals of the murine left ventricle (LV) at the high frame rate of 8 kHz. Due to high frame rate of the data acquisition system and high resolution of the ultrasound system, myocardial elastography at both high temporal and spatial resolution were obtained. Results from nine normal and seven infarcted myocardia were finally compared in order to study the potential application of myocardial elastography in infarct detection.

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II. METHODS

A. Animal Preparation

Nine wild-type mice were anesthetized with 125 mg/kg intraperitoneal injection of tribromoethanol. The ultrasound probe was placed on the mouse chest using degassed ultrasound gel (Aquasonic 100, Parker Laboratories, Inc., Orange, Fairfield, NJ) as a coupling medium. The ECG signal was obtained from the electrode pads on the mouse platform. After the mice were scanned, a myocardial infarction (MI) was induced by permanent ligation of the left anterior descending coronary artery (LAD) in mice after left-sided thoracotomy. Two mice died due to the surgery complications while the remaining seven mice (MI mice) were scanned one day after the operation.

B. Data Acquisition

The high frame-rate data acquisition system previously developed [8] was used in this study. A 30-MHz ultrasound probe (Vevo 770, VisualSonics Inc., Toronto, ON, Canada) was placed on the mouse chest in the parasternal position to obtain a longitudinal (long-axis) view of the LV of the heart. The field of view was 12 mm x 12 mm, the axial resolution was equal to 50 μm, and the lateral resolution was equal to 115 μm.

In the EKV™ (ECG-based kilohertz visualization) mode provided by the imaging system, the transducer worked on a line-by-line basis. The ultrasound echo signals were recorded at a pulse-repetition frequency (PRF) of 8 kHz at each position of the transducer. A two-channel, 14-bit waveform digitizer (CompuScope 14200, Gage Applied Technologies, Inc., Lachine, QC, Canada) was used to synchronously acquire the RF signals of the ultrasound scanner and the associated ECG at 160 MS/s. After data acquisition, the acquired RF signals were gated between two consecutive R-waves in the ECG to provide by the imaging system, the transducer worked on a pulse-repetition frequency (PRF) of 8 kHz at each position of the transducer. A two-channel, 14-bit waveform digitizer (CompuScope 14200, Gage Applied Technologies, Inc., Lachine, QC, Canada) was used to synchronously acquire the RF signals of the ultrasound scanner and the associated ECG at 160 MS/s. After data acquisition, the acquired RF signals were gated between two consecutive R-waves in the ECG to provide by the imaging system, the transducer worked on a pulse-repetition frequency (PRF) of 8 kHz at each position of the transducer. A two-channel, 14-bit waveform digitizer (CompuScope 14200, Gage Applied Technologies, Inc., Lachine, QC, Canada) was used to synchronously acquire the RF signals of the ultrasound scanner and the associated ECG at 160 MS/s. After data acquisition, the acquired RF signals were gated between two consecutive R-waves in the ECG to reconstruct the RF image sequence for a complete heart cycle at the extremely high frame rate of 8 kHz [8].

C. Data Processing

The axial displacement was estimated off-line using the normalized cross-correlation function [4]. The RF window size was equal to 480 μm, while the window overlap was equal to 95%, deemed high enough to retain the high axial resolution [9]. To reduce the noise amplification effect of the gradient operator in strain calculation, the linear Savitzky-Golay differentiation filter of length 7 (140 μm) [10] was used to estimate the axial strains.

The aforementioned displacements and strains were the instantaneous or incremental displacements and strains occurring between two consecutive frames. Using the incremental displacements over one cardiac cycle, the points in the LV wall could be tracked automatically [11-12]. Therefore, the incremental displacements and strains corresponding to the preset points could be extracted. By accumulating these incremental displacements and strains, the cumulative displacement and strains were obtained and represented the total motions and deformations from the first frame (corresponding the beginning of the cardiac cycle), respectively.

In the displacement, strain or correlation images, only the results in the region of interest (ROI) were shown for better interpretation. A ROI was first determined by a 40-50 point selection manually done in the first frame of B-mode ciné-loop (reconstructed from the RF image sequence). The selected points were close to the myocardial boundaries (endocardium and epicardium). Using the estimated displacement field, these points could then be tracked over the entire cardiac cycle [11-12], providing the updated ROI’s corresponding to different phases.

III. RESULTS

The incremental displacement images (a, c) and elastograms (b, d) of a normal myocardium in the phases of systole (a, b) and diastole (c, d), respectively, are shown in Fig. 1(a). The results were color-coded and superimposed onto the grayscale B-mode image. In the displacement images, positive displacements (in red) denoted motions towards the transducer (located at the top) and negative displacements (in blue), motions away from the transducer. In the elastograms, positive and negative values (in red and blue, respectively) represented stretching (i.e., thickening) and compression (i.e., thinning) of the myocardium, respectively. The red dot in the ECG trace below indicated time in the cardiac cycle when the image above it corresponded to.

![Figure 1](image_url)

During diastole of the normal ventricle, as shown in Fig. 1(a), the myocardium contraction was clearly visible, with the interventricular septum (IVS) moving away from the transducer and the posterolateral wall (PLW) moving towards the transducer. In the diastolic phase (Fig. 1(c)), displacements were in the opposite direction from those during systole, while the myocardium relaxed. On the elastogram at the systolic phase (Fig. 1(b)), positive strains were visible in both the IVS and PLW, indicating thickening of the myocardium. In the diastolic phase (Fig. 1(d)), the compressive strains in the IVS and PLW denoted thinning of the myocardium.

Figure 2 depicts the displacement images (a, c) and elastograms (b, d) of an infarcted myocardium in the systolic
phase (a, b) and diastolic phase (c, d), respectively. The LAD ligation induced an anterior apical infarction, which was found in the anterior apical region of the infarcted heart. The displacements and strains in the infarcted myocardium were smaller than those in the normal myocardium (Fig. 2). In addition, the strain in the infarcted region was found to undergo opposite strain compared to the surrounding region (i.e., border zone) (Figs. 2(b) and (d)).

![Image](https://via.placeholder.com/150)

Figure 2. Incremental displacements (a, c) and elastograms (b, d) of an infarcted myocardium at systole (a, b) and diastole (c, d)

Figure 3 compares the cumulative displacements images and elastograms of the normal myocardium, infarct and border zone at end-systole. The infarcted myocardium (infarct and border zone) underwent smaller cumulative displacements and strains than the normal myocardium. In addition, the infarct was clearly detected with negative strains compared to the neighboring regions. The cumulative strains in the normal myocardium, infarct and border zone were measured as 53±5%, -6±1% and 17±2%, respectively.

![Image](https://via.placeholder.com/150)

Figure 3. Cumulative displacements (a, c) and elastograms (b, d) at end-systole of the normal (a, b) and infarcted (c, d) myocardia

Figure 4 compares the cumulative displacement and strain variation with time, of the normal myocardium, infarct and border zone, respectively. The profiles were calculated by averaging over a small region in the septum where the displacements and strains were relatively uniform. The drift in the cumulative displacement and strain profiles had been corrected on the assumption that the drift occurred linearly throughout a cardiac cycle [13]. Lower motion and deformation could be seen in the infarcted myocardium (infarct and border zone). In addition, compared to those of the normal myocardium and border zone, cumulative strains in the infarcted zone had opposite signs (Fig. 4(d)), e.g., the infarct had negative cumulative strains during systole, while the normal myocardium and border zone had positive cumulative strains, and vice versus during diastole.

As shown in Fig. 5, preliminary statistical results from nine normal and seven infarcted mice showed the cumulative strains at end-systole (i.e., total deformation during systole) were equal to 56±13%, -4±32% and 22±19% for the normal myocardia, infarcts and border zones, respectively. The ability to differentiate the infarcts from normal myocardia was tested by using statistical comparisons of the results. Student’s t-test confirmed that the difference in cumulative strains at end-systole between the infarcts and normal myocardia were significant (p< 0.001). In addition, the t-test also indicated the significant difference between the infarcts and the border zones (p< 0.10).

![Image](https://via.placeholder.com/150)

Figure 4. Cumulative displacement (a) and strain (b) profiles

![Image](https://via.placeholder.com/150)

Figure 5. Averages and standard deviations of the cumulative strains at end-systole of the normal myocardia, infarct and border zones.

### IV. DISCUSSIONS

Using retrospective ECG gating, RF signals of the murine LV were acquired at an extremely high frame rate of 8 kHz. The estimated displacements occurred within a short time of 0.125 ms, resulting in a high temporal resolution. In elastography, sonographic and elastographic axial resolutions were equivalent [9], i.e., the elastographic axial resolution was equal to 50 μm in our study. From the incremental
displacements of the infarct during ejection, the minimum detectable displacements of this system were close to 0.05 µm.

Displacement estimates did not help differentiate between contraction and simple rotation or translation of hearts. In addition, they cannot differentiate passive motion (e.g., tethering) from active contraction. As shown in Fig. 4, the cumulative displacements of the infarct and border zone were reduced. However, it was difficult to detect the exact location of the infarct from the displacement images. Consequently, strain estimates, which represented the deformation of the myocardium, were found to be more effective in detecting the infarct. From the cumulative elastograms (Fig. 4 (d)), the infarct was detected by localized thinning of myocardium during systole. In addition, the cumulative elastograms represented the total deformation during systole and were less dependent on the selected RF image frame. Therefore, the cumulative elastograms were deemed capable of providing the most reliable measurements of the regional myocardial deformation.

Negative cumulative systolic strains were found in the infarcts, confirming the results of finite-element simulations based on canine data [14]. After LAD ligation, the myocardium could not contract sufficiently and the infarcts might not contract actively. During systole, the muscle surrounding the infarct stretched and tethered the infarct in the circumferential direction. Along the radial direction, the infarcted muscle was shown to undergo a negative strain (thinning) to balance the circumferential lengthening. This might explain the negative strain in the infarcted region during systole. On the other hand, the interaction between the infarct and the border zone also affected the motion and deformation of the latter. As a result, the displacements and strains in the border zone (Figs. 4 and 5) were shown to be smaller than those of the normal myocardium (Fig. 3). Further work should be carried out to verify this assumption.

Statistical analysis of the cumulative strains from normal (n=9) and infarcted (n=7) mice showed a larger variation in the infarcts. This was due to the variability in the performance of each LAD ligation and differences in the responses of the myocardium to the ligation among different mice. In addition, the motion and deformation of the infarcted myocardium were smaller and hence more susceptible to arbitrary noise. The results also depended on the image plane selected; it was difficult to scan different mice using exactly the same sonographic view. Despite this variation, the statistical significance in differentiating the infarcted myocardium from the normal one was high (p<0.001).

V. CONCLUSION

In this paper, a high-resolution ultrasound system and a high frame-rate acquisition system based on retrospective ECG gating were used to acquire the RF signals of mice hearts. RF signals were acquired at extremely high frame rate (up to 8 kHz). The incremental and cumulative, displacement images and elastograms were obtained with the myocardial elastographic technique, providing the regional information of myocardium motion and deformation. Taking advantage of the high resolution of the transducer and the high precision in displacement estimation using RF tracking, a high axial resolution of 50 µm was achieved. The detectable displacement was as small as 0.05 µm. To our knowledge, this is the first time that myocardial elastography was achieved at such high spatial (50 µm) and temporal (0.125 ms) resolution as well as high precision (minimum displacement ≈ 0.05 µm). Results from normal and infarcted murine myocardia indicated reduced motion and deformation in the one-day-old infarcts. Results showed that the infarcts underwent thinning rather than thickening during systole. Preliminary statistical results from nine normal and seven infarcted mice indicated myocardial elastography was feasible in assessing myocardial function as well as detecting and localizing myocardial infarction in vivo.

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REFERENCES