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In-Vivo Magnetic Resonance Elastography to Estimate Left Ventricular Stiffness in a Myocardial Infarction Induced Porcine Model

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Abstract

Purpose—To estimate change in left ventricular (LV) end-systolic and end-diastolic myocardial stiffness (MS) in pigs induced with myocardial infarction (MI) with disease progression using cardiac magnetic resonance elastography (MRE) and to compare it against *ex-vivo* mechanical testing, LV circumferential strain and MRI relaxometry parameters (T1, T2, and extracellular volume fraction (ECV)).

Methods—MRI (1.5T) was performed on 7 pigs, before surgery (Bx), and 10 (D10) and 21 (D21) days after creating MI. cardiac MRE-derived MS was measured in infarcted region (MIR) and remote region (RR), and validated using mechanical testing-derived MS obtained post-sacrifice on D21. Circumferential strain and MRI relaxometry parameters (T2, T1, and ECV) were also obtained. Multi-parametric analysis was performed to determine correlation between cardiac MRE-derived MS and i) strain, ii) relaxometry parameters, and iii) mechanical testing.

Results—Mean diastolic (D10:5.09±0.6kPa; D21:5.45±0.7kPa) and systolic (D10:5.72±0.8kPa; D21:6.34±1.0kPa) MS in MIR were significantly higher ($p<0.01$) compared to mean diastolic

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(D10:3.97±0.4kPa; D21:4.12±0.2kPa) and systolic (D10:5.08±0.6kPa; and D21:5.16±0.6kPa) MS in RR. The increase in cardiac MRE-derived MS at D21 (MIR) was consistent and correlated strongly with mechanical testing-derived MS ($r(\text{diastolic})=0.86$; $r(\text{systolic})=0.89$). Diastolic MS in MIR demonstrated a negative correlation with strain ($r=0.58$). Additionally, cardiac MRE-derived MS demonstrated good correlations with post-contrast T1 ($r(\text{diastolic})=-0.549$; $r(\text{systolic})=-0.741$) and ECV ($r(\text{diastolic})=0.548$; $r(\text{systolic})=0.703$), and no correlation with T2.

Conclusion—As MI progressed, cardiac MRE-derived MS increased in MIR compared to RR, which significantly correlated with mechanical testing-derived MS, T1 and ECV.

Keywords

Myocardial Stiffness; Cardiac Magnetic Resonance Elastography; cardiac MRE; Myocardial Infarction

INTRODUCTION

Myocardial Infarction (MI), which results from occlusion of a coronary artery, accounts for 1.5 million annual incidences in US (1). Coronary artery occlusions result in an inadequate supply of oxygenated blood to the myocardium leading to myocardial necrosis. This affects cardiac mechanics by causing regional myocardial dysfunction (2) and increase in myocardial stiffness (MS) (3,4), which may eventually trigger heart failure (5). Therefore, understanding and quantifying cardiac mechanics (related to myocardial stiffness) associated with the onset, progression, and remodeling of MI (6) is important for developing effective treatment to prevent heart failure.

Currently, pressure-volume analysis (P-V) and biomechanical testing are used to quantify mechanical properties of the myocardium. Previous studies using P-V analysis have shown that left ventricular (LV) compliance decreased following MI (4). Furthermore, studies using biomechanical testing have shown a regional elevation in MS at the site of MI (3). Although, these techniques have successfully shown the change in mechanical properties of the myocardium post-MI, both these techniques are invasive in nature and hence clinically challenging. Therefore, a non-invasive tool to quantify regional MS may provide an alternative to the currently used techniques.

Strain-based cardiac MRI (spatial modulation of magnetization tagging (7), displacement encoding with stimulated echo (8), strain encoding (9)) techniques used for quantitative evaluation of regional myocardial contractile performance does not account for the effects of variable loading conditions. As a result these techniques provide relative strain measurements that do not reveal the true intrinsic mechanical properties of the myocardium.

Recently, with the advent of cardiac magnetic resonance elastography (cardiac MRE), a phase-contrast-based MRI technique to non-invasively quantify myocardial stiffness has become feasible (10–17). This study created a MI induced porcine model and aimed to 1) use cardiac MRE to estimate MS in both infarcted and remote normal regions during disease progression; 2) validate cardiac MRE measurements against results from ex-vivo mechanical testing; and 3) measure circumferential strain, T1, T2 and extracellular volume fraction

(ECV) in both infarcted and remote non-infarcted regions and compare the measurements to cardiac MRE-derived MS.

MATERIALS AND METHODS

All animal procedures were performed with the approval of the university's institutional animal care and use committee. Seven juvenile pigs (serially studied at three time-points, i.e. $n=21$) weighing ~70 lbs were used for this study. MI was created by injecting ethanol into the mid left-anterior-descending artery (distal to the first diagonal branch) and post-surgical coronary angiograms were acquired to confirm complete occlusion (18).

MR Imaging Timeline

MRI was performed on all the animals prior to coronary occlusion for baseline (Bx) measurements, and then 10 days (D10), and 21 days (D21) post-MI with the imaging parameters remaining same for all time points. These two post-MI time points were specifically selected to monitor the mechanical properties of the myocardium as the non-reperfused MI evolved from acute/early reparative state (necrosis with edema, neutrophilic infiltration, myocyte fragmentation, peripheral phagocytosis, granulation with loose collagen deposition) during weeks 1–2 to sub-acute/early fibrotic phases (progressively dense collagen deposition) from weeks 3–8 (19–21).

Animal Preparation for MRI

Imaging was performed in animals under anesthesia (induced using ketamine (20mg/kg) and acepromazine (0.5mg/kg) and maintained using isoflurane (1–5%). The animals were placed feet-first supine on the MR table and a custom-built driver system was used to induce external vibrations as shown in Figure 1.

Image Acquisition

All image acquisition was performed under breath-hold using a clinical 1.5-Tesla MRI scanner (Avanto, Siemens Healthcare, Erlangen, Germany). Cardiac triggered segmented balanced steady-state free precession cine sequence was implemented to acquire vertical, horizontal long-axis views and short-axis views covering the heart. These cine images were used to plan all the other scans. Imaging parameters included: echo time (TE)/repetition time (TR)=1.49/27.36 ms; field of view (FOV)=300×300 mm²; imaging matrix (IM)=256×256; slice thickness (ST)=6mm; flip angle (FA)=46°; cardiac phases (CP)=30; GRAPPA acceleration factor (AF)=2.

A retrospective pulse-gated, segmented cine gradient recalled echo (GRE) cardiac MRE sequence was used to obtain short-axis slices covering the entire LV (10,15–17). Imaging parameters for cardiac MRE included: TE/TR=9.71/12.5 ms; FOV=384×384 mm²; IM=128×128; ST=8mm; FA=15°; CP=8; number of segments=8 (positive and negative encoding); temporal resolution=12.5ms for acquiring each k-space line; GRAPPA AF=2; excitation frequency=80Hz; encoding frequency=160Hz; phase offsets=4. Image acquisition time was ~16–20sec which varied based on the heart rate.

A prospectively gated GRE based cardiac tagging sequence was used to acquire short-axis slices covering the entire heart. Imaging parameters included: TE/TR=3.42/19.47 ms; FOV=300×300 mm²; IM=224×168; ST=8mm; FA=8°; CP=25;

Short-axis delayed enhancement (DE) imaging was performed using a T1-weighted phase-sensitive IR sequence across the entire heart, 8 minutes post-injection of contrast agent in order to confirm the region of MI. Imaging parameters for PSIR included: TE/TR=4.34/662 ms; FOV=360×292 mm²; IM=192×160; ST=8mm; FA=25°; CP=1;

Quantitative parametric mapping was performed to analyze the change in T1, T2 properties and ECV fraction at different stages of disease progression. Blood samples were drawn to measure the hematocrit fraction for ECV calculations. Short-axis T2 maps were acquired to identify the presence of any myocardial edema as a result of MI. Imaging parameters included: TE/TR=1.37/229.36 ms; FOV=360×270 mm²; IM=192×160; ST=8mm; FA=35°; CP=1; GRAPPA AF=2. Short-axis T1 modified Look-Locker inversion recovery sequence was acquired pre-contrast (T1_{pre}) and then re-acquired post-contrast (T1_{post}), 10 mins after injection of contrast agent to investigate fibrosis and estimate ECV. Imaging parameters for T1 maps were similar to T2 maps except TE = 1.01 ms and TR = 255.46 ms.

Post-contrast images (i.e. DE and T1_{post}) were acquired after manual injection of a rapid bolus of Gadobenate Dimeglumine (MultiHance, Bracco Diagnostics, Princeton, NJ) followed by a 20 mL saline flush. The dosage was varied by the animal's weight at a rate of 0.2 mL/kg.

Image Processing

Cardiac MRE Analysis—The cardiac MRE magnitude images were used to identify the systolic and diastolic cardiac phases based on the smallest and largest LV blood pool, respectively. Next, cardiac MRE wave images were masked to extract the LV and then analyzed using MRELab (Mayo Clinic, USA) to estimate systolic and diastolic MS. A directional-filter in 8 radial directions was applied to remove the reflected waves and a 4th order Butterworth band-pass filter with cutoffs 0.384 m/FOV to 0.0096 m/FOV was used to remove the longitudinal component of motion. This filtered wave data was then inverted by applying a 3D local frequency estimation algorithm (LFE) (22). Using DE images as reference, the MI (hyper-intense) region (MIR) and non-infarcted (unenhanced region opposite to MIR) remote region (RR) was identified on the stiffness maps and MS at D10 and D21 in MIR and RR was reported. For Bx measurements (used as controls) regions were identified on the stiffness maps that corresponded to MIR and RR on the D10/D21 DE images and an average from both these regions were reported as the Bx MS to be consistent with other time points.

Cardiac Strain Analysis—Tagged images were analyzed using commercial HARP software (Diagnosoft, Palo Alto, California). The slice with the strongest infarct was selected and endocardial and epicardial contours were drawn on the end-systolic phase. Circumferential Eulerian strain was automatically calculated for the different segments of the heart. For Bx strain measurements the average from all the segments was reported. For

D10 and D21, segments corresponding to RR and MIR were selected to report the strain in the infarcted and remote zones.

Quantitative Mapping (MRI Relaxometry Parameters)—Regions on the relaxometry maps both for Bx and post-MI (D10 and D21) were defined based on the DE images (as described for the cardiac MRE analysis) and the mean values were reported. ECV was calculated as the ratio of the myocardial and blood pool (blood T1 was estimated from T1* maps) relaxation rates ($R1$) calibrated by blood hematocrit using the following equation:

$$\Delta R1 = \frac{1}{T1(Post)} - \frac{1}{T1(Pre)} \quad (1)$$

$$ECV = (1 - \text{hematocrit}) \times \frac{\Delta R1_{myo}}{\Delta R1_{blood}} \quad (2)$$

Mechanical Testing

After imaging on D21 animals were sacrificed using Euthasol (to arrest the heart in systole), and the hearts were extracted and prepared for biomechanical testing. Approximately $35 \times 10 \times 3 \text{ mm}^3$ cuts were made on the remote and infarcted region (wall thinning in infarcted region made it difficult to keep the width constant), and multiple infarcted and remote samples were obtained for repeated measurements. The samples were stored in a hypotonic cardioplegic/lactated ringers solution (3) till the availability of the material-testing-system. A servohydraulic material-testing-system (Bionix 858, MTS System Corp, MN) was used to determine the stiffness of the infarcted and remote specimens. Each specimen was secured in cryogrips. No preload was used for this study to avoid damage to the specimens. Uniaxial ramped load with displacement control at 10mm/min was applied until failure with continuous recording of load and displacement. Peak load to failure and structural stiffness was determined for each sample from the load-displacement curve by measuring maximum load and linear slope of the curve respectively.

Statistical Analysis

Data analyses were performed by using SAS-9.4 software (SAS, Inc; NC). Longitudinal measures of stiffness were analyzed by mixed effect models, accounting for the association of the same measure at different time points from the same animal (23). These models included location (MIR or RR) as a covariate and days post-surgery as independent variable of interest and allow subject specific intercepts and slopes. The slopes, means and standard errors were estimated and compared by using these models. Correlations between both systolic and diastolic MS and circumferential strain, T2, T1_{post}, ECV, and mechanical testing were assessed by Pearson's correlation method. $P < 0.05$ was considered statistically significant.

RESULTS

Out of 7 animals scanned, one died on D10 and since no complete post-surgical time point was collected on this animal, this animal was excluded from any analysis. Out of the remaining 6 animals analyzed for this study, one animal died after the D10 scan, and therefore, results for D21 was unavailable. These animals died due to surgical complications.

Cardiac MRE Stiffness Estimates

Figure 2 shows the diastolic and systolic magnitude image, wave propagation, and stiffness maps at Bx and D21. Mean (from all animals) diastolic MS at Bx was 3.87 ± 0.4 kPa. At D10, and D21 mean diastolic MS was 5.09 ± 0.6 kPa and, 5.45 ± 0.7 kPa, respectively in MIR and 3.97 ± 0.4 kPa, and, 4.12 ± 0.2 kPa, respectively in RR (Figure 3a). Mean (from all animals) systolic MS at Bx was 4.98 ± 0.7 kPa. At D10, and D21 mean systolic MS was 5.72 ± 0.8 kPa and, 6.34 ± 1.0 kPa, respectively in MIR and 5.08 ± 0.6 kPa, and, 5.16 ± 0.6 kPa, respectively in RR (Figure 3b). The results demonstrate that MS was significantly higher in MIR as compared to RR both at D10 (diastole: $p=0.0003$; systole: $p=0.0318$) and D21 (diastole: $p=0.0002$; systole: $p=0.0018$). Slope analyses indicated that as the MIs evolved, both diastolic and systolic MS increased in MIR (diastolic: slope=1.58, $p<0.0001$; systolic: slope=1.43, $p=0.0025$) but it did not show any significant change in RR.

Cardiac Strain Analysis

Figure 4a shows the box plot for circumferential strain in MIR and RR at different time points (Bx, D10, and D21). The mean circumferential Eulerian strain at Bx was -7.41 . Strain measurements in MIR at D10 and D21 were -1.10 , and -0.18 , respectively, while that in RR at D10, and D21 were -8.26 , and -9.50 , respectively. The mean strain in RR was significantly higher than the mean in MIR both at D10 ($p<0.0001$) and D21 ($p<0.0001$). Additionally, slope analysis indicated significant decrease in strain from Bx to D21 in MIR (slope=7.23, $p=0.0002$). Figure 4b and 4c shows correlation of circumferential Eulerian strain in the MIR with diastolic MS, and systolic MS, respectively. While circumferential Eulerian strain exhibits a significant negative correlation with diastolic MS ($r=0.58$, $p=0.044$), no significance was observed with systolic MS ($r=0.31$, $p=0.254$).

Quantitative Mapping (MRI Relaxation Parameters)

Figure 5 shows the DE image, T2, and $T1_{\text{post}}$ maps in an animal both at Bx and D21 (in a slice containing the infarct). As shown, at Bx uniform intensity was observed in the DE image (Figure 5a), T2 (Figure 5b) and $T1_{\text{post}}$ (Figure 5c) map. However, on D21 hyper-enhancement was present in MIR for both DE image (Figure 5d) and T2 map (Figure 5e) while reduced intensity was observed in $T1_{\text{post}}$ (Figure 5f) map.

T2 Map Measurements

Mean (from all animals) T2 estimate at Bx was 44.6 ± 2.1 ms. At D10, and D21 T2 values were 59.8 ± 5.4 ms and, 68.4 ± 9.7 ms, respectively in MIR and 45.1 ± 1.4 ms, and, 47.2 ± 1.6 ms, respectively in RR (Figure 6a). The results show that the T2 values in RR was significantly lower than MIR both at D10 ($p=0.0003$) and D21 ($p<0.0001$). Additionally, slope analyses indicated that as the disease progressed from Bx to D21 the mean T2 measure increased

significantly (slope=23.62, $p<0.0001$) in the MIR, however, no change ($p=0.31$) was observed in the RR.

T1 Map Measurements

Mean (pooling all animals) $T1_{\text{post}}$ measurement at Bx was $525.9\pm37.3\text{ms}$. At D10, and D21 $T1$ values were $390.0\pm15.2\text{ms}$, and, $361.7\pm22.9\text{ms}$, respectively in MIR and $543.7\pm32.6\text{ms}$, and, $527.1\pm29.1\text{ms}$, respectively in RR (Figure 6b). The results demonstrated that $T1_{\text{post}}$ values in MIR was significantly lower compared to RR both at D10 ($p<0.0001$) and D21 ($p<0.0001$). Furthermore, as the disease progressed from Bx to D21, the $T1_{\text{post}}$ values reduced significantly in MIR (slope= -158.9 , $p<0.0001$) but not in RR ($p=0.6$).

ECV Measurements

Mean ECV from all animals at Bx was $25.6\pm1.1\%$. At D10 and D21 ECV estimates were $48.1\pm6.3\%$, and $52.5\pm6.6\%$, respectively, in MIR and, $25.2\pm2.4\%$, and $26.6\pm3.0\%$, respectively, in RR (Figure 6c). An intra-time point comparison indicated that the ECV measures in MIR were significantly ($p<0.0001$) higher than RR both at D10 and D21. Additionally, the results also revealed that while there was no change in ECV with disease progression in RR ($p=0.6409$, slope analysis), in MIR ECV increased significantly (slope= 26.95 , $p<0.0001$) with time.

Quantitative Mapping Correlation Analysis

Figure 7 shows the MIR correlation maps between cardiac MRE-derived stiffness (both systolic and diastolic) and MRI relaxometry parameters. Although there is a positive trend no significant correlation was observed between $T2$ and either diastolic (Figure 7a) or systolic MS (Figure 7d). Significant inverse correlation was observed between $T1_{\text{post}}$ and both diastolic ($r=-0.549$, $p=0.022$) (Figure 7b) and systolic ($r=-0.741$, $p=0.0007$) (Figure 7e) MS. A significant good positive correlation was observed between ECV and both diastolic ($r=0.548$, $p=0.023$) (Figure 7c) and systolic ($r=0.703$, $p=0.0016$) (Figure 7f) MS.

Mechanical Testing

Figure 8a demonstrates that the mechanical testing-derived stiffness from the excised MIR samples is higher compared to RR samples. Mean stiffness across all animals in MIR is 1.698 N/mm , which is nearly twice as much as RR (0.868 N/mm) ($p=0.005$). Correlation maps (Figure 8b) indicate that there was a strong positive correlation between mechanical testing-derived stiffness and both cardiac MRE-derived diastolic ($r=0.86$, $p<0.0001$) and systolic ($r=0.89$, $p<0.0001$) MS.

DISCUSSION

Overall Summary

This study demonstrated that cardiac MRE can non-invasively quantify alteration in MS in a MI induced porcine model. The results indicated that over a 3week period, the infarcted region underwent a steady increase in MS both at diastole and systole, as opposed to the remote region where MS remained preserved. This increase in cardiac MRE-derived

stiffness was validated by uniaxial *ex-vivo* mechanical testing, indicating that cardiac MRE has the potential to be used as a diagnostic tool to investigate the mechanical alterations triggered by MI. Additionally, multi-parametric analysis indicated that cardiac MRE-derived stiffness has i) negative correlation (diastolic MS) with strain measurements; ii) positive trend with T2 measurements; iii) significant inverse correlation to T1_{post} measurements; and iv) strong positive correlation to ECV measurements.

Cardiac MRE-Derived Stiffness

As the MI progressed from Bx to D21 an increase in MS was observed in MIR. To the best of our knowledge, there is only one other study that used cardiac MRE (implemented phase gradient *inversion* of the radial component of motion on 1D linear line profiles) to quantitate MS in a MI model (13). Since our study used 3D LFE (previously used to estimate MS in *in-vivo* volunteers) (17) that incorporated complete 3D wave propagation information as opposed to the previous study that used 1D wave profiles, a direct comparison of stiffness values is not possible. However, it is important to note that both the studies observed increased MS in MIR when compared to RR at D21. Since, the previous study, estimated MS post 3 weeks of inducing MI, Bx and D10 measurements were unavailable for comparison. Our findings also demonstrated that throughout systolic MS was higher compared to diastolic MS, an outcome that was consistent with previously reported findings (22).

Cardiac Strain Analysis

Circumferential strain measurements were significantly reduced in MIR both at D10 and D21, which is consistent with results obtained by another research group (24). Since, circumferential strain is a measure of circumferential shortening the value is negative during systole in the normal myocardium, and higher negative strain values indicating better compliance. In an infarcted myocardium since due to increased stiffness the myocardium's ability to contract is compromised, the amount of deformation in the infarcted myocardium is reduced which in turn reduces the strain measurements. This implies that a negative correlation should be expected between MS and strain. Although we observed a significant negative correlation between diastolic MS and strain, but only a negative trend was observed with systolic MS. It is important to note that diastolic MS reports the true intrinsic passive stiffness of the myocardium (i.e. without active contraction and ~zero LV pressure), whereas, systolic MS contains effects from active contraction and pressure. Isolating pressure effects from the systolic MS measurements is very challenging, and this could potentially contribute to the insignificant association between circumferential strain and systolic MS.

Quantitative Mapping (MRI Relaxometry Parameters)

The significant increase in the T2 value from Bx to D10 and D21 in MIR and the hyper-intensity noticed in the T2 map images confirm presence of myocardial edema which is consistent with results reported in previous studies (25). Despite increase in T2 values no significant correlation was observed with cardiac MRE-derived MS. This can be attributed to the fact that physiological response of MI is different from one animal to the other and each animal could be at a very different inflammatory stage. The accurate time point to

investigate the change in T2 estimate would be within the first week from the onset of MI when the myocardium is at its peak inflammatory stage with maximum edema. Since the inflammatory stage subsides after fibrosis starts, the increase in MS observed in this study could be a result of fibrosis and not inflammation which is further confirmed by the T1 and ECV correlation maps. Due to fibrosis caused by MI, the contrast agent was trapped in the infarcted myocardium which was reflected as reduced T1 values in the T1_{post} maps as observed by other groups (26,27). This correlated well (inverse correlation) with cardiac MRE-derived MS justifying that fibrosis and mechanical properties are interdependent. The increase in the ECV with disease progression observed in MIR is consistent with fibrosis as stated in previous works (28,29). The positive correlation between both systolic and diastolic MS and ECV indicates change in mechanical properties of the myocardium is directly dependent on the alteration of the extracellular matrix content. An increase in ECV and decrease in T1 might indicate the alteration of extracellular matrix content and fibrosis content, respectively, but may not provide the information of myocardial compliance. Therefore, it is also important to estimate MS.

Mechanical Testing

A significant increase in stiffness was observed in MIR compared to RR which was consistent with previously reported study (3). A strong positive correlation was observed between mechanical testing-derived stiffness and cardiac MRE-derived stiffness. Since mechanical testing is invasive in nature, requires technical precision and is therefore clinically inefficient; the strong correlation between cardiac MRE and mechanical stiffness indicates that cardiac MRE can be potentially used as a non-invasively alternative to estimate MS in MI.

Limitations

There are some limitations in our study. First, the time period between sacrifice and mechanical testing varied from 1 day to 2 weeks based on the availability of the mechanical testing system. This limitation was addressed by freezing (-20°C) the specimens in Ringer's solution so that the mechanical properties remained preserved. Second, the loading frequencies of cardiac MRE and mechanical testing are very different. Third, due to oblique cuts in the excised specimen and wall thinning due to pathology, the width of the samples might not have been uniform throughout, and the geometric measurements such as widths and lengths used to estimate stiffness might not be very precise. Fourth, failure often occurred at regions other than the narrowest location and these factors could affect the peak stress values, which could eventually affect the stiffness measurements. Despite these factors a significantly strong positive correlation coefficient was observed between mechanical testing-derived stiffness and cardiac MRE-derived stiffness. Fifth, from the DE images it was observed that some of the infarcts had regions of dark myocardium that could be a result of microvascular obstruction. Therefore, while estimating the MRI relaxometry parameters these regions were excluded from the ROI. Sixth, systolic and diastolic phases were investigated instead of end-diastole and end-systole due to following reasons: a) the temporal resolution was not high enough to capture the precise end-systolic or end-diastolic phase (22); and b) due to ST segment elevation and arrhythmia noticed post-infarction, motion artifacts prevailed in the end-systolic and end-diastolic phases due to miss-triggering.

Therefore, systolic and the diastolic cardiac phases were selected, since those images were collected from a more stable section of the cardiac cycle. Finally, the myocardium is known to be anisotropic due to complex fiber architecture. Hence, to estimate the true stiffness of the myocardium a 3D anisotropic *inversion* that accounts for the fiber orientation and as well as the geometry is needed and is currently outside the scope of this manuscript. Therefore, the reported MS measurement in the current manuscript is not an absolute measure and is termed to be an “effective” estimate. Despite these limitations this study showed significant increase in stiffness in MIR compared to RR both at systole and diastole.

In conclusion, this study demonstrated that the effective cardiac MRE-derived MS in MIR is higher than RR, an inference that was validated using mechanical testing-derived stiffness. Significant negative correlation was observed between cardiac MRE-derived diastolic MS and circumferential strain measurements in MIR. Additionally, significant correlation was also observed in MIR between cardiac MRE-derived MS (diastolic and systolic), and $T1_{\text{post}}$ and ECV confirming that cardiac MRE can be used as a potential alternative to mechanical testing.

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Figure 1. Experimental Set-Up

The passive driver is placed on the animal's anterior chest wall. Acoustic waves are generated using a custom-built active driver that is placed outside the scan room. Waves from the acoustic driver are transmitted to the passive driver via the plastic tube.

Figure 2. Cardiac MRE Images

Baseline: Magnitude image: (a) diastole (g) systole; Wave propagation (four phase offsets) in x-direction: (b–e) diastole (h–k) systole; Stiffness maps (f) diastole (l) systole. **Day 21:** (m) DE image showing MIR (red) and RR (green); Magnitude image delineating MIR the RR (n) diastole (t) systole; Wave propagation (four phase offsets) in x-direction: (o–r) diastole (u–x) systole; Stiffness maps (s) diastole (y) systole.

Figure 3. Cardiac MRE-Derived Stiffness

Box plots showing **a)** systolic and **b)** diastolic stiffness in MIR and RR at Bx, D10 and D21. Stiffness at MIR is higher than RR. Stiffness increased significantly from Bx to D21 in MIR (*) but did not change in RR (#).

Figure 4. Circumferential Strain

a) Box plot showing circumferential strain at Bx, D10 and D21. Strain decreased significantly in MIR compared to RR. From Bx to D21, RR did not change (#) but MIR decreased progressively (*). Correlation maps between circumferential strain and **b)** diastolic ($p=0.04$) and **c)** systolic stiffness ($p=0.25$). Moderate negative correlation was observed with diastolic MS and systolic MS.

Figure 5. DE Image and Corresponding Relaxometry Maps

(a) Baseline DE image shows no enhancement; (d) D21 DE image shows hyper-enhancement (white arrow), 8mins after contrast injection. (b) Baseline T2 map with uniform intensity; (e) D21 T2 map shows patchy hyper-intensity (white arrow). (c) Baseline T1_{post} (10 mins after contrast injection) map shows uniform intensity; (f) D21 T1_{post} map shows reduced intensity (white arrow).

Figure 6. Relaxometry Analysis

Box plot shows relaxometry parameters in MIR and RR at Bx, D10 and D21. **a)** T2 values increased significantly in MIR as compared to RR both at D10 and D21 **b)** T1_{post} values decreased significant in the MIR as compared to RR both at D10 and D21. **c)** ECV increased significantly in MIR compared to RR both at D10 and D21.

Figure 7. Correlation Analysis between cardiac MRE-Derived MS and Relaxometry Parameters

No significant correlation ($r < 0.5$) was observed between T2 and **a)** diastolic MS ($p = 0.09$) and **d)** systolic MS ($p = 0.53$). Good inverse significant correlation was observed between ($r < -0.5$) T1_{post} and **b)** diastolic MS ($p = 0.022$) and **e)** systolic MS ($p = 0.0007$). Good positive significant correlation ($r > 0.5$) was observed between ECV and **c)** diastolic MS ($p = 0.023$) and **f)** systolic MS ($p = 0.0016$).

Figure 8. Mechanical testing results and statistics

a) Box plot shows stiffness in infarcted and remote myocardium using uniaxial mechanical testing. **b)** Correlation map between mechanical testing-derived MS and both cardiac MRE-derived systolic and diastolic stiffness demonstrated good significant correlation ($r>0.8$).