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Temporal Changes in Infarct Material Properties: An In Vivo Assessment Using Magnetic Resonance Imaging and Finite Element Simulations

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Abstract

Background.—Infarct expansion initiates and sustains adverse left ventricular (LV) remodeling after myocardial infarction (MI) and is influenced by temporal changes in infarct material properties. Data from ex vivo biaxial extension testing support this hypothesis; however, infarct material properties have never been measured in vivo. The goal of the current study was to serially quantify the in vivo material properties and fiber orientation of infarcted myocardium over a 12-week period in a porcine model of MI.

Methods.—A combination of magnetic resonance imaging (MRI), catheterization, finite element modeling, and numeric optimization was used to analyze posterolateral MI. Specifically, properties were determined by minimizing the difference between in vivo strains and volume calculated from MRI and strains and volume predicted by finite element modeling.

Results.—In 1 week after MI, the infarct region was found to be approximately 20 times stiffer than normal diastolic myocardium. Over the course of 12 weeks, the infarct region became progressively less stiff as the LV dilated and ejection fraction decreased. The infarct thinned by nearly half during the remodeling period, and infarct fiber angles became more circumferentially oriented.

Conclusions.—The results reported here are consistent with previously described ex vivo biaxial extension studies of infarct material properties and the circumferential change of collagen orientation in posterolateral infarcts. The current study represents a significant advance in that the method used allows for the serial assessment of an individual infarct in vivo over time and avoids the inherent limitations related to the testing of excised tissues.

Infarct expansion initiates and sustains adverse left ventricular (LV) remodeling after myocardial infarction (MI), resulting in ventricular dilatation, loss of global contractile function, and symptomatic heart failure. Infarct expansion that occurs concomitantly with

the onset of ischemia is readily explained by loss of active contraction of the infarct region. Immediately after the onset of ischemia, the infarct region ceases to contract and is subjected to the hemodynamic load produced by the remainder of the ventricle. This abnormal loading results in thinning and stretching of the infarct and in increased mechanical stress in the perfused border zone region adjacent to the infarct. During the ensuing hours, days, and weeks, a complex wound healing process occurs, which further affects infarct material properties. These time-dependent changes determine the extent of infarct expansion and, therefore, the fate of the entire LV. In spite of the central role that infarct material properties must play in the remodeling process, few quantitative data exist that describe their temporal changes after MI. Gupta and colleagues [1] used biaxial force-extension testing to assess the material properties of sheep infarct tissue over a 6-week period using excised postmortem specimens. These authors demonstrated that the infarct became more compliant between 2 and 6 weeks in spite of increasing collagen content as the ventricle progressively dilated. Although the report by Gupta and colleagues [1] 2 decades ago represented a seminal advance in our understanding of the biomechanical response of the LV to MI, it has not been possible to confirm these investigators' results in vivo. We have recently described a technique that uses LV strain measurements based on magnetic resonance imaging (MRI) and finite element (FE) simulations [2] that allow for the serial assessment of infarct material properties over time in the same subject. We applied this new approach to study a posterolateral infarct in pigs. Our results confirm and expand those reported by Gupta and colleagues [1] and support the inhibition of infarct expansion as an important therapeutic goal in the prevention of adverse LV remodeling after MI.

Material and Methods

All of the animals used in this study received care in compliance with the protocols approved by the Institutional Animal Care and Use Committee at the University of Pennsylvania in accordance with the National Institutes of Health "Guide for the Care and Use of Laboratory Animals" (NIH publication 85-23, revised 1996).

Myocardial Infarction

Seven male Yorkshire pigs (43 ± 9 kg at the time of infarction) were enrolled in the study. The animals were first sedated with intramuscular ketamine injection (25–30 mg/kg), intubated, and mechanically ventilated. General anesthesia was maintained with mixed isoflurane (1.5% to 3.0%) and oxygen, which was delivered by volume-controlled ventilation (tidal volume 10 to 15 mg/kg). After left thoracotomy, animals underwent selective ligation of the circumflex artery, its branches, or both to create a posterolateral infarct constituting approximately 20% to 25% of the LV (Fig 1). Akinesis of the affected wall was confirmed with intraoperative echocardiography. Ten custom 2-mm platinum markers were positioned around the infarct periphery to assist in infarct localization during later MRI acquisitions and postprocessing. After hemodynamic and electrophysiologic stability were ensured, all animals were then recovered. The animals were sacrificed 12 weeks after infarction.

Magnetic Resonance Imaging

All animals underwent serial cardiac MRI to assess global ventricular function, infarct thinning and expansion, and in vivo myocardial stress-strain relationships (Fig 1). Baseline MRI scans were performed 5 to 7 days before infarction, with subsequent scans performed 1, 4, 8, and 12 weeks after infarction. General anesthesia was maintained for the entirety of the imaging procedures, as described above. A high-fidelity, MRI-compatible pressure transduction catheter (Millar Instruments; Houston, TX) was inserted into the carotid artery and guided by fluoroscopy into position in the LV. This allowed for pressure gating and was used to trigger the tagging sequence to occur at isovolumic relaxation (downsloping LV pressure), as opposed to the onset of systole, which is typically done by electrocardiographic triggering. As a result, the tags remain strong throughout diastole. MRI was performed by use of a 3T Seimens Trio A Tim Magnetom scanner (Seimens; Malvern, PA). The animals underwent prospectively gated three-dimensional (3D) steady-state free precession (SSFP) cine MRI for volumetric analysis with use of the following parameters: field of view, 300×244 ; acquisition matrix, 192×156 ; repetition time, 3.11 ms; echo time, 1.53 ms; bandwidth, 1,184 Hz/pixel; slice thickness, 4 mm; averages, 2. Fifteen minutes after the intravenous injection of 0.1 mmol/kg gadobenatidimeglumine (MultiHance; Bracco Diagnostics, Princeton, NJ), infarct location and wall thickness were visualized by use of a 3D late gadolinium enhanced (LGE) spoiled gradient echo sequence with the following parameters: field of view, 350×350 ; acquisition matrix, 256×256 ; repetition time, 591.28 ms; echo time, 2.96 ms; inversion time, 200 to 300 ms; flip angle, 25° , averages, 2. Regional LV strain was assessed by use of a diastolic 3D SPAtial Modulation of Magnetization (SPAMM) tagged sequence with the following parameters: field of view, 260×260 ; acquisition matrix, 256×128 ; repetition time, 34.4 ms; tag spacing, 6 mm; bandwidth, 330 Hz/pixel; slice thickness, 2 mm; averages, 4. The images were archived and stored offline for postprocessing [3].

Postprocessing Images

Infarct and remote wall thickness were measured from cine MRI at end diastole. Thirty random radially oriented spokes (extending from endocardium to epicardium) were positioned throughout each 3D infarct area by use of ImageJ software (NIH; Bethesda, MD). Platinum markers and LGE images were used to identify infarct boundaries (Fig 1). Infarct and remote wall thickness was calculated at each time point from average spoke length. The LV end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF) were calculated throughout the entire cardiac cycle from segmented images using inputs of in-plane and through-plane spatial resolution (Fig 1).

Regional strain measurements were calculated from 3D SPAMM acquisitions using an optical flow technique. Raw short-axis 3D SPAMM images were first manually cropped to include only the left ventricle from the apex to the mitral annulus. Epicardial and endocardial contours were manually segmented at the early diastolic reference state using ImageJ software (National Institutes of Health [NIH]; Bethesda, MD). Reference state image masks were then created from segmented contours to isolate LV myocardium. A custom optical flow plug-in for ImageJ was used to derive 3D displacement flow fields and strain tensors from the tagged images through end diastole [4]. Endocardial contours were also

performed at end diastole for LV volume calculations, and endocardial/epicardial infarct boundaries were identified with use of the previously placed platinum epicardial markers. Synchronous LV pressure was matched to the images over the entire cardiac cycle.

Assessment of In Vivo Material Properties

The in vivo material properties (ie, stiffness) of both the remote and infarct regions were estimated by a combination of MRI data, FE simulations, and numeric optimization. This technique was validated in a previous study that used animal-specific data from pigs 1 week after posterolateral MI. The details were described by Mojsejenko and colleagues [2]. Briefly, early diastole was taken to be the reference state for the animal-specific ventricular FE models because LV pressure is at a minimum. The FE models were generated by fitting the early diastolic endocardial and epicardial contours with 3D surfaces (Rapidform; INUS Technology, Inc., Sunnyvale, CA). The FE mesh was produced by filling the volume between these surfaces with hexahedral trilinear elements (TrueGrid; XYZ Scientific, Inc., Livermore, CA). The infarct and remote regions were designated as two separate materials, allowing for different properties to be assigned to each, and were defined by 3D curves created from MRI-derived infarct contours. Myofiber angles were assigned for each hexahedral element by use of a custom MATLAB code and were assumed to vary linearly in the transmural direction [5]. Remote angles were fixed to be 83° at the endocardial surface and -37° at the epicardial surface with respect to the circumferential direction [6, 7] for the baseline, 1-week, and 4-week cases; but for the 8-week and 12-week cases the remote fiber angles were set at -27° at the epicardium and 88° at the endocardium [8]. The infarct fiber angles were assigned by use of an optimization algorithm as described below. The endocardial wall was loaded with a pressure boundary condition, which was based on the time course of the measured animal-specific diastolic pressure. Figure 2 shows an example of the surface generation and resulting FE model for a representative case.

The diastolic material properties of both the infarct and remote regions were described by a nearly incompressible, transversely isotropic, hyperelastic constitutive model [9], which was implemented by use of the nonlinear FE software LS-DYNA (Livermore Software Technology Corporation; Livermore, CA). The key equations can be found in Mojsejenko and colleagues [2]. The material parameters C , b_f , b_t , b_{fs} , are constants that describe the nonlinear diastolic myocardial tissue properties. It should be noted that b_f governs the stiffness in the fiber direction, b_t the stiffness in the cross-fiber and radial directions, and b_{fs} the stiffness in the shear directions.

Subsequently, the software LS-OPT (Livermore Software Technology Corporation; Livermore, CA) was used to determine the optimal set of myocardial material parameters in both the infarct and remote regions, and also the epicardial and endocardial fiber angles in the infarct [2]. This was accomplished by using a genetic algorithm to minimizing the error (mean squared error, MSE) between the FE model predicted strain and the in vivo MRI measured strain. Genetic algorithms perform well as global optimizers, whereas gradient-based methods can get stuck in local optima in the exploration of a large parameter space. In addition to the diastolic strain inputs, constraints on LV cavity volume were incorporated into the MSE calculation to ensure better agreement. The material parameters obtained from

the optimization were then input into an equibiaxial extension simulation to obtain representative stress-strain curves of the infarct and remote regions. By use of a custom MATLAB code, stress was calculated for a range of strain values to facilitate a clearer interpretation of differences in myocardial tissue properties over the 12-week period after infarction.

Statistics

All data are presented as mean $\pm$ standard error of the mean (SEM) unless otherwise noted. The LV volume, wall thickness, and regional strain comparisons were performed by the use of unpaired two-tailed *t* tests. A *p* value less than 0.05 was considered statistically significant.

Results

Global Remodeling of LV Volume

Overall, the LV volumes tended to progressively increase over time after infarction (Fig 3). Comparison of the post-MI time points relative to the baseline volumes (EDV, 69.4 ± 7.9 mL; ESV, 35.5 ± 5.7 mL) indicated that the majority of the ventricular expansion occurred within the first week after MI (EDV, 104.8 ± 6.5 mL; ESV, 65.5 ± 6.6 mL). All post-MI volumes (EDV and ESV) over the entire 12-week time course are shown in Figure 3 and were statistically greater ($p < 0.05$) than the baseline volumes. Ventricular function, quantified by EF, was found to decrease after infarction (Fig 3). Relative to baseline ($51.2 \pm 3.5\%$), the EFs were statistically different ($p < 0.05$) at all time points after MI. The EF 1 week after infarction was $38.1 \pm 2.9\%$.

Structural Remodeling of Infarct

Infarct wall thickness was assessed in vivo over the 12-week time course after MI by use of cine MRI (Fig 4). The end-diastolic infarct wall thickness continuously decreased over the entire time course. This trend was confirmed qualitatively in the LGE MR images. All infarct thicknesses were significantly different ($p < 0.05$) from the baseline posterolateral wall thickness (baseline, 9.6 ± 0.2 mm), ranging from 7.2 ± 0.5 mm 1 week after MI to 4.2 ± 0.3 mm 12 weeks after MI. As a comparison, the remote wall thickness remained unchanged over the 12-week study (average over time points, 9.6 ± 0.1 mm), and there was no statistically significant difference in comparison with the baseline value at each time point (baseline, 9.6 ± 0.2 mm).

Mechanical Remodeling of Infarct

Animal-specific FE models were loaded with an applied ventricular pressure and used to predict end-diastolic strains within the LV wall at each time point (Fig 5). The constitutive model material parameters (C , b_f , b_t , b_{fs}) within the infarct and remote regions, along with the infarct fiber angles, were determined through optimization by matching the FE strain to the strain measured from MRI, with an additional constraint to match the LV volume within $\pm 5\%$. The remote material parameters are given in Table 1, and the infarct parameters and fiber angles are reported in Table 2. Because it is difficult to interpret the nonlinear constitutive parameters by themselves, simulated equibiaxial tests were used to estimate

stress over a given range of strain values and to generate stress-strain curves relative to the fiber and cross-fiber directions. This was done in an effort to better understand differences in passive myocardial properties over the 12-week period. Examination of the stress-strain curves revealed stiffening of the infarct region 1 week after MI induction in comparison with baseline (Fig 6). With each subsequent time point, the infarct became progressively less stiff. These trends were consistent between the fiber and cross-fiber directions, but the stiffness in the fiber direction was greater than in the cross-fiber direction at each time point. This trend was also seen in the remote region, but the increase in stiffness was less substantial.

The moduli of the stress-strain curves were quantified over different strain ranges (0–0.05 and 0.05–0.10) for further analysis of the changes in stiffness over the 12-week period. Infarct stiffness was greater in the fiber direction relative to the cross-fiber direction, and this stiffening response progressively declined over time (Fig 7). It should be noted that the mean infarct stiffness 1 week after MI was roughly 20 times greater than the baseline myocardial stiffness, compared with the 12-week case, where the stiffness was roughly three times greater.

The MSE values, which assess the amount of error between the FE-model predicted and the MRI-derived strains, ranged from 6.1 ± 1.5 to 11.3 ± 9.5 (Table 2). The average MSE values are consistent with those of previous studies [2, 10] and were comparable with one another over the different time points. This indicates good agreement between the model predictions and experimentally measured data. The infarct fiber angles were found to range from $-14.89 \pm 21.30^\circ$ to $-33.54 \pm 25.73^\circ$ at the epicardial surface over the 12-week period, which shows deviation from the baseline value of -37° toward a more circumferential orientation. Additionally, the infarct fiber angles at the endocardial surface varied from $43.56 \pm 2.50^\circ$ 1 week after MI to $9.18 \pm 15.42^\circ$ 12 weeks after MI, showing a more substantial deviation from the baseline value of 83° toward a more circumferential orientation.

Comment

This study describes the first serial in vivo assessment of infarct material properties and fiber orientation in the remodeling LV after MI. The mean infarct stiffness 1 week after MI was approximately 20 times greater than the stiffness of passive (diastolic) myocardium that was measured before infarction. Between 1 week and 12 weeks, post-MI infarct stiffness decreased progressively to approximately three times the stiffness of passive uninjured myocardium as the LV dilated and EF decreased.

The 20-fold increase in stiffness between normal (uninjured) passive myocardium and the infarct 1 week after MI must be carefully considered. Before MI, all segments of the myocardium stiffen considerably as the LV contracts during systole. Immediately after coronary occlusion, the infarct area ceases to contract and, at least during the very early post-MI period, maintains essentially normal diastolic properties as the remainder of the LV contracts. Although not assessed in this study, the difference between normal systolic and diastolic myocardial stiffness is substantial, likely differing by one or two orders of magnitude [11]. This precipitous reduction in relative stiffness in the infarct region results in its immediate expansion and in dilatation of the LV chamber. The relative stiffening of the

infarct region occurring during the first week after MI is likely due to edema and inflammation, which only partially and temporarily ameliorates infarct expansion before the infarct becomes progressively less stiff as the infarct heals and LV dilatation progresses.

The results reported here are consistent with those in the ex vivo biaxial extension studies of infarct material properties conducted by Gupta and colleagues [1] more than two decades ago. Both studies confirm the importance of temporal changes in infarct materials and infarct expansion on the post-MI LV remodeling process. In addition to material properties, the changes in endocardial and epicardial fiber angles reported in the current study are consistent with the circumferential change of collagen orientation in posterolateral infarcts in 3-week post-MI pigs reported by Holmes and colleagues [12] and posterolateral infarcts in rats reported by Fomovsky and colleagues [13]. The current study represents a significant advance in that the method used allows for the serial assessment of an individual infarct in vivo over time and avoids the inherent limitations related to the testing of tissue excised from postmortem specimens. Moreover, this technique is able to capture changes in both material stiffness and fiber orientation after MI, yielding a more accurate representation of MI mechanics.

Our group has had a long-term interest in the prevention of infarct expansion as a therapeutic goal to prevent or limit post-MI LV remodeling and heart failure [14]. We initially tested numerous infarct wrapping techniques to prevent infarct expansion, but more recently, in an attempt to develop less invasive therapeutic strategies, we have focused on the use of injectable biomaterials to stiffen the infarct to reduce expansion [15]. Although these studies have been encouraging, few data exist to aid in determining the optimal mechanical properties of the injected materials. This study and subsequent studies using the imaging and modeling algorithms described here will help in the design and engineering of optimized injectable biomaterials.

The current study does have important limitations. First, although infarct stiffness decreased over time in all subjects, there was significant variability between individuals. Second, only posterior infarcts were studied; infarcts in this location expand less and are associated with less adverse remodeling relative to apical infarcts. Additional studies with larger animal numbers and apical infarcts are planned and should help to address these limitations in the near future.

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Fig 1.

In vivo function was assessed in an established porcine posterior infarct model. (A) Magnetic resonance imaging (MRI) was performed at baseline and 1, 4, 8, and 12 weeks after myocardial infarction (MI). (B) Infarction was induced by ligation of the LCX and select OM, with MRI-compatible markers attached around the boundary of MI. MRI data were analyzed to assess (C) global cardiac structure and function from cine MRI, (D) infarct expansion from DCE MRI, and (E) myocardial wall function from SPATial Modulation of Magnetization—tagged MRI. Scale bar = 1 cm. (DCE = delayed contrast enhanced; LAD = left anterior descending artery; LCX = left circumflex artery; OM = obtuse marginal branch artery; PD = posterior descending artery.)

Fig 2.

Finite element models were generated by fitting magnetic resonance imaging—derived endocardial and epicardial contours with (A B) 3-dimensional surfaces to represent the animal-specific geometry and filling the myocardial space with hexahedral brick elements. (C) The boundary between the infarct (blue) and remote (red) region was defined using 3-dimensional curves created from MRI-derived infarct contours. (D) Myofiber angles varied transmurally and were fixed for the remote region and assigned by optimization for the infarct region with respect to the circumferential direction.

Fig 3.

Infarction leads to (A, B) increased left ventricular volumes relative to baseline (BL) and (C) decreased ejection fraction 1, 4, 8, and 12 weeks after infarction. Data presented as mean $\pm$ standard error of the mean. All data (end-diastolic volume, end systolic volume, ejection fraction) statistically significant from baseline ($p < 0.05$).

Fig 4.

(A) Infarct wall thickness was measured in vivo throughout the study by analyzing cine magnetic resonance images at end diastole. (B) In vivo assessment shows thinning of the myocardial wall in the infarct region after myocardial infarction. Data presented as mean $\pm$ standard error of the mean. All results for (B) are statistically significant relative to baseline (BL) and for infarct (INF) vs remote (REM) thickness at each time point ($p < 0.05$). Scale bar = 1 cm.

Fig 5.

(A) Representative finite element models of the same animal at baseline (BL) and 1, 4, 8, and 12 week after MI. (B) Short axis views taken from roughly the same position at midventricle demonstrate thinning of the infarct region (blue) over time. The model geometry is based on early diastole.

Fig 6.

Equibiaxial extension tests were simulated by use of the material parameters determined from the optimization. Mean stress-strain plots of (A, B) the infarct and (C, D) remote regions in the (A, C) fiber and (B, D) cross-fiber directions over time. (BL = baseline.)

Fig 7.

Quantification of the modulus from the simulated equibiaxial extension tests at different strain ranges. The moduli are given in the (A, C) fiber and (B, D) crossfiber directions for both the remote and infarct regions over time. Data presented as mean $\pm$ standard error of the mean. BL = baseline. * $p < 0.05$ vs baseline myocardium.

Table 1.**Optimization Results for Remote Region**

Remote	Baseline	Time Point			
		1 Week	4 Weeks	8 Weeks	12 Weeks
C (kPa)	0.39 ± 0.10	2.59 ± 2.13	1.85 ± 2.66	0.52 ± 0.18	0.41 ± 0.24
b _f	72.03 ± 29.63	29.44 ± 39.21	30.15 ± 39.21	37.67 ± 28.94	29.52 ± 11.15
b _t	5.08 ± 4.53	11.04 ± 15.64	9.28 ± 4.21	17.39 ± 15.75	11.14 ± 7.92
b _{fs}	36.69 ± 18.23	19.35 ± 16.46	28.45 ± 18.67	23.12 ± 15.77	30.86 ± 15.45

Values are reported as mean ± 1 standard deviation.

b_f = stiffness in the fiber direction;

b_{fs} = stiffness in the shear directions;

b_t = stiffness in the cross-fiber and radial directions.

Table 2.**Optimization Results for Infarct Region**

Infarct	Baseline	Time Point			
		1 Week	4 Weeks	8 Weeks	12 Weeks
C (kPa)	0.39 ± 0.10	1.48 ± 1.40	6.08 ± 4.03	9.38 ± 5.10	4.01 ± 2.34
b _f	72.03 ± 29.63	171.53 ± 39.78	13.77 ± 12.54	15.28 ± 19.71	19.01 ± 31.15
b _t	5.08 ± 4.53	24.22 ± 19.62	6.58 ± 5.96	8.32 ± 4.59	8.07 ± 5.64
b _{fs}	36.69 ± 18.23	22.25 ± 17.55	8.64 ± 2.51	25.27 ± 27.41	17.19 ± 18.13
epicardial angle (°)	-37	-14.89 ± 21.30	-23.00 ± 25.01	-18.15 ± 21.81	-33.54 ± 25.73
endocardial angle (°)	83	43.56 ± 2.50	35.66 ± 21.41	26.69 ± 14.61	9.18 ± 15.42
MSE	8.64 ± 1.53	7.43 ± 4.02	7.62 ± 2.08	11.31 ± 9.46	8.14 ± 3.63

Values are reported as mean ± 1 standard deviation.

b_f = stiffness in the fiber direction;

b_{fs} = stiffness in the shear directions;

b_t = stiffness in the cross-fiber and radial directions;

MSE = mean squared error.