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Longitudinal Reinforcement of Acute Myocardial Infarcts Improves Function by Transmurally Redistributing Stretch and Stress

A wide range of emerging therapies, from surgical restraint to biomaterial injection to tissue engineering, aim to improve heart function and limit adverse remodeling following myocardial infarction (MI). We previously showed that longitudinal surgical reinforcement of large anterior infarcts in dogs could significantly enhance systolic function without restricting diastolic function, but the underlying mechanisms for this improvement are poorly understood. The goal of this study was to construct a finite element model that could match our previously published data on changes in regional strains and left ventricular function following longitudinal surgical reinforcement, then use the model to explore potential mechanisms for the improvement in systolic function we observed. The model presented here, implemented in FEBIO, matches all the key features of our experiments, including diastolic remodeling strains in the ischemic region, small shifts in the end-diastolic pressure–volume relationship (EDPVR), and large changes in the end-systolic pressure–volume relationship (ESPVR) in response to ischemia and to patch application. Detailed examination of model strains and stresses suggests that longitudinal reinforcement reduces peak diastolic fiber stretch and systolic fiber stress in the remote myocardium and shifts those peaks away from the endocardial surface by reshaping the left ventricle (LV). These findings could help to guide the development of novel therapies to improve post-MI function by providing specific design objectives.

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Introduction

Myocardial infarction (MI), commonly known as a heart attack, affects over 1 million Americans each year [1]. Myocardial infarctions occur when the blood flow to a region of the heart is interrupted, leading to cardiomyocyte death and loss of regional contractile function. Infarction alters the local and global mechanics, initiating a process of adverse growth and remodeling in the surviving myocardium. Here, we define growth as an increase in mass and remodeling as a change in shape or material properties, with the understanding that in the heart these processes often occur in tandem. Over time, the mechanics of the heart is further altered as a stiff collagen scar replaces dead myocytes during the post-MI healing process. Adverse growth and remodeling lead to progressive dilation of the left ventricle (LV), continued deterioration of pump function, and eventually the development of heart failure. Restoring or at least improving cardiac function early in the healing process could help promote long-term survival and deter the development of heart failure. Accordingly, a wide range of therapies that aim to improve function or limit LV remodeling

have been proposed, ranging from surgical reinforcement or restraint to augmentation with tissue-engineered patches to injection of various biomaterials [2–5].

Our lab previously developed a promising approach to improving pump function acutely following a large anteroapical infarction by selectively reinforcing the infarct in the longitudinal direction [6]. We began by conducting a computational screen for how infarct material properties impact pump function [7]. In agreement with the prior work by other groups [8,9], the finite element model used in that screen predicted that isotropic stiffening of an infarct would improve systolic function at the cost of restricting filling, resulting in no net gain in stroke volume at matched pressures. On the other hand, the model predicted that an anisotropic infarct with high longitudinal stiffness but low circumferential stiffness would maximize stroke volume, primarily by improving filling. We then validated the model prediction in a canine model of MI by acutely sewing a modified Dacron patch onto the surface of the heart. Volumes, pressures, and infarct region segment lengths were measured at baseline pre-MI, acutely post-MI, and after application of the patch. These data were used to compare the cardiac output (CO) at matched pressures between each of the conditions. As expected, acute ischemia shifted the CO-end-diastolic pressure (EDP) curve downward, so that the

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Fig. 1 Model construction pipeline: (a) representative example of magnetic resonance imaging segmentation of the endocardium and epicardium in short axis slices of the LV; all MRI data were taken from a previous study by Clarke et al. [10]. (b) Cubic Hermite surfaces are fitted to the segmented slices for each specimen. (c) Individual specimen surfaces are discretized into an average surface and (d) scaled down to create an unloaded mesh that preserves the initial wall volume. (e) The unloaded mesh is then used to create three distinct finite element models of the baseline, acutely ischemic, and patch-reinforced LV. (f) The patch reinforces the ischemic region on the anterior wall of the LV.

cardiac output was reduced at matched filling pressures. Anisotropic reinforcement shifted the CO–pressure curve upward, closer to baseline, indicating an increase in the CO at matched pressures [6].

While our experimental studies validated the overall model prediction that longitudinal infarct reinforcement improved LV function, the mechanisms underlying the improvement in the experiment did not match the original model predictions. In contrast to the model predictions, the primary effect of experimental longitudinal reinforcement was on systolic function, indicated by a leftward shift in the end-systolic pressure–volume relationship (ESPVR) after application of the patch. Another surprise was that local segment lengths tracked by sonomicrometry increased at matched EDPs acutely post-MI, indicating apparent softening in the infarct region that was not predicted in the original model but was significantly modified by application of the patch. Thus, the aim of the current modeling study was to re-examine the mechanisms by which longitudinal reinforcement of acute, anteroapical myocardial infarcts leads to improvement in stroke volume at matched pressures. We tested the potential mechanisms by creating a new set of finite element models of the canine LV tuned to capture the behavior observed in the experiments. Our new models improve upon the previous computational study [7] by allowing differences in passive material behavior between healthy and ischemic myocardium; by carefully fitting geometry, passive material properties, and active material properties to experimental data from our laboratory; and by simulating full pressure–volume loops over a range of loading conditions to map diastolic and systolic pressure–volume relationships. Our results suggest that longitudinal reinforcement reduces peak diastolic fiber stretch and systolic fiber stress in the remote myocardium and shifts those peaks away from the endocardial surface by reshaping the left ventricle. This redistribution shifts the ESPVR leftward, indicating improved ejection against a given systolic pressure, with little impact on diastolic filling.

Methods

Model Construction. We built new finite element models of the acutely ischemic canine LV by creating an average geometry

from CINE magnetic resonance imaging (MRI) scans of 16 different dogs taken 48 h post-MI (Fig. 1(a)) as part of a prior study [10]. For each scan, we segmented the endocardial and epicardial contours in 7–10 short-axis slices acquired at end systole (ES) using the open-source software SEGMENT (v1.9 R3767¹) running in MATLAB (R2014b, Mathworks), and fitted the endocardial and epicardial surfaces in prolate spheroidal coordinates with meshes of 4×4 bicubic Hermite elements (Fig. 1(b)) [11]. We exported points at specified angular coordinates from each of the 16 fitted surfaces and then calculated the average endocardial and epicardial points to define an average geometry in prolate spheroidal coordinates (Fig. 1(c)). We then used linear interpolation between the endocardial and epicardial points to define mesh nodes across the wall. The nodes were converted to Cartesian coordinates, and a hexahedral element connectivity matrix was defined for a finite element model implementation in FEBIO 2.6.4.² We used an additional ring of rigid-body elements adjacent to the basal-most endocardial layer to simulate a valve ring and a ring of pentahedral rigid-body elements to seal the apex. Our final finite element mesh consisted of 9680 nodes and 7840 linear elements (Fig. 1(e)). In each layer of the LV, we assigned a fiber direction ranging from -60 deg on the epicardium to 60 deg on the endocardium [12]. We simulated loading by applying a specified pressure to the endocardial surface of the LV, using the Pardiso solver in FEBIO to solve for the equilibrium configuration at each step.

Because the MRI contours used to make the model were obtained at end systole, we scaled the fitted mesh to better approximate the unloaded geometry of the LV. This unloaded geometry was taken to be stress-free in all simulations. We scaled the unloaded geometry in prolate spheroidal coordinates by multiplying the focus of each layer of nodes across the wall by scaling factors that increased evenly in value from the endocardial to epicardial surface, thus obtaining a smaller cavity volume while maintaining the same wall volume. We iterated through the scaling process until we obtained an unloaded geometry that resulted

¹<http://medviso.com/segment/>

²<https://feb.io/>

in simulated end-diastolic volumes (EDV) similar to the experimental data (Fig. 1(d)). The new unloaded model had a cavity volume of 30 mL and was used in the optimization scheme described below to obtain passive material parameters.

The mechanics of an acutely ischemic region are typically simulated by turning off active contraction but assuming that the passive material properties are unchanged, since inflammation and wound healing have not yet begun. However, our previous canine study found significant increases in local end-diastolic segment lengths measured by sonomicrometry during acute ischemia at matched EDP [6]. This unexpected behavior is particularly interesting because longitudinal reinforcement, which successfully improves pump function, also reverses this diastolic remodeling in the infarct region. While the exact mechanism by which the ischemic region appears to soften is not fully understood, we suspect that the loss of perfusion in that region leads to an

immediate thinning of the wall and thus higher stresses and stretches at matched EDP [13]. Alternatively, loss of pressurization of the coronary vessels may reduce passive stiffness directly [14]. For the purpose of our finite element models, we can capture this apparent softening in the infarct region either by changing the local wall thickness or by changing the passive material properties of the infarct region; here, we chose to alter the passive material properties.

A nearly-incompressible transversely isotropic Mooney–Rivlin (TIMR) material available in FEBIO was used to simulate normal myocardium, ischemic myocardium, and the patch used for surgical reinforcement. This material combines the standard strain-energy function for an isotropic Mooney–Rivlin material with a term that depends nonlinearly on strain along one defined fiber direction (Eq. (1)). The strain-energy function of the TIMR material includes five user-defined parameters: C_1 (isotropic term), C_2

Fig. 2 Model parameter fitting: (a) data used for fitting were taken from a previous study by Fomovsky et al. [6] and included EDVs for baseline (1), acute ischemia (2), and longitudinal patch (3); circumferential (4) and longitudinal (5) remodeling strains; and the change in base-apex (6) and septal-lateral (7) dimensions between acute ischemia and baseline. (b) Mean EDV (line) $\pm$ 1SD range (filled boxes) for baseline, acute ischemia, and longitudinal patch and the corresponding model values (circles) at matched experimental pressures. (c) Mean remodeling strain (line) $\pm$ 1SD range (filled boxes) for acute ischemia and longitudinal patch in the circumferential and longitudinal directions. Model values (open boxes) correspond to the range of values for 20 elements within the center of the infarct area in the midendocardial layer. (d) Mean percent change (line) $\pm$ 1SD range (filled boxes) for base-apex and septal-lateral dimensions between acute ischemia and baseline at ED and corresponding model values (circles) at matched experimental pressures. (e) Schematic showing how the remodeling deformation relates the baseline and ischemic region deformations at a matched pressure.

Table 1 Active contraction parameters

$T_{\max}$	135.7 kPa
Ca_0	4.35
$Ca_{\max}$	4.35
β	4.75
l_0	1.58
l_{ref}	1.58
α_1	75
A_1	50
a	0.5

(isotropic term), C_3 (linear fiber term), C_4 (exponential fiber term), and K (bulk modulus). In order to reduce the number of free parameters in our optimization, we fixed the values of two of these parameters for all simulations. Based on prior work [15,16] showing that functions of the first and fourth invariants of the right Cauchy–Green deformation tensor (I_C and IV_C in Eq. (1)) provide a good description of the passive behavior of myocardium, we set C_2 to 0, eliminating the contribution of the second invariant II_C . In addition, based on a parameter sensitivity analysis that revealed that the value of K had little effect on the material behavior during passive inflation as long as $K \gg C_1$, we set $K = 100$ for all simulations. The remaining three parameters were optimized for three different cases: normal myocardium (baseline), acutely ischemic myocardium (acute ischemia), and the longitudinally stiff patch (longitudinal patch).

$$W = C_1(I_C - 3) + C_2(II_C - 3) + F(\sqrt{IV_C}) + \frac{K}{2}[\ln(J)]^2$$

$$\frac{\partial W}{\partial I_C} = C_1 \quad \frac{\partial W}{\partial II_C} = C_2 \quad \frac{\partial W}{\partial IV_C} = \frac{1}{\lambda_1} C_3(e^{C_4(\lambda_1 - 1)} - 1) \quad (1)$$

Material Property Optimization. The three materials of interest were optimized in two steps: first, normal and ischemic myocardium parameters were fitted together using data from the published experimental results; then, the longitudinally stiff patch was added by modifying the top layer of elements in the infarct region, and its material properties were fitted using additional experimental data taken following patch application. We optimized the normal and ischemic myocardium material parameter sets simultaneously by comparing the baseline and acute ischemia model results to six experimental values from our previously published experiments [6]: end-diastolic volumes (EDV_{Base} , EDV_{Isch}) for baseline and acute ischemia at their respective average end-diastolic pressures, which allow us to match the overall compliance of the heart; circumferential (E_{circ}) and longitudinal (E_{long}) remodeling strains in the anterior midwall at a matched pressure of 12 mmHg, which capture the apparent softening of the ischemic myocardium; and the changes in base-apex (L_{BA}) and septal-lateral (L_{SL}) cavity dimensions between baseline and ischemia at a matched end-diastolic pressure of 12 mmHg, which provide information on the anisotropy of the normal myocardium. Model volumes were calculated using the nodal positions of the second layer of nodes from the endocardium, to match the positions of the sonomicrometry crystals used to measure the experimental volumes. As shown in Eqs. (2) and (3) and diagrammed in Fig. 2, the remodeling strain reflects the remodeling deformation

occurring from baseline to acute ischemia, which we calculated by inflating both the baseline model and the model with acutely ischemic properties in the infarct region from unloaded to 12 mmHg. Because both models share a common unloaded state, we can use a multiplicative decomposition to relate the deformation occurring in acute ischemia, F_{Ischemia} , to the baseline deformation, F_{Baseline} , through the remodeling deformation, $F_{\text{Remodeling}}$. Model strains were averaged across 20 elements in the infarct region that corresponded to the experimental locations of the sonomicrometry crystals. For the patch model, the optimization criteria include three metrics: end-diastolic volume at the experimentally measured end-diastolic pressure (EDV_{patch}) and the circumferential (E_{circ}) and longitudinal (E_{long}) remodeling strains at a matched pressure of 12 mmHg, reflecting the diastolic strain differences induced by patch placement relative to ischemia alone.

In order to force outputs from the optimized model to remain within one standard deviation of the experimental means, we selected a nonlinear error measure for use in the optimization. We defined an exponential error function (Eq. (4)) using scaled Z scores. We calculated a traditional Z score by dividing the difference between the model output and the experimental mean by the experimental standard deviation, then subtracted one and multiplied the result by a scaling term to more heavily penalize values beyond one standard deviation. Thus, an output that matched the experimental mean yielded an error of 1/1000, an output one standard deviation from the mean yielded an error of one, and an output two standard deviations from the mean yielded an error value of 1000. This approach allowed us to both heavily penalize model outputs that fell outside one standard deviation of the experimental means and to weigh data with different orders of magnitude equally in the fit.

$$\mathbf{E}_{\text{Remodeling}} = \frac{1}{2} \left(\mathbf{F}_{\text{Remodeling}}^T \mathbf{F}_{\text{Remodeling}} - \mathbf{I} \right) \quad (2)$$

$$\mathbf{F}_{\text{Remodeling}} = \mathbf{F}_{\text{Ischemia}} \mathbf{F}_{\text{Baseline}}^{-1} \quad (3)$$

$$\text{Error}_i = e^{\left(\ln(1000) \left(\frac{|\text{Mean}_i - \text{Model}_i|}{\text{SD}_i} - 1 \right) \right)} \quad (4)$$

Total Error = $\sum_i \text{Error}_i$, where i = optimization criteria

Active Contraction and Pressure–Volume Loops. We implemented a custom active contraction plugin that combines the length-dependent behavior currently used in FEBIO [17] and a modified force–velocity relationship based on the fading-memory formulation proposed by Hunter et al. [18]. The tension generated in our active contraction module (Eq. (5)) is the product of three distinct components: a time-varying normalized activation, $e(t)$, that defines the time course of force generation throughout the cardiac cycle; an instantaneous length-dependent term that scales the peak possible isometric tension based on the current fiber stretch; and a force-velocity term that dampens the instantaneous force generation based on the rate of shortening of the fibers. The parameters used in our active contraction module are presented in Table 1. The total fiber stress is the sum of the passive fiber stress, calculated from the strain-energy density function in Eq. (1), and the tension generated in our active contraction module (Eq. (6)).

Table 2 Passive material parameter values

	Normal myocardium	Ischemic myocardium	% Δ	Patch	% Δ
C_1 (kPa)	0.5	0.25	−50%	3.1	+520%
C_2 (kPa)	0	0	0%	0	0%
C_3 (kPa)	0.0005	0.00035	−30%	10	+1.9 × 10 ⁶ %
C_4 (unitless)	50	45	−10%	70	+40%
K (kPa)	100	100	0%	100	0%

Fig. 3 Full cardiac cycle simulations: (a) average experimental pressure versus time curves (solid lines) for baseline, acute ischemia, and longitudinal patch. These pressures are used as the loading conditions for the finite element models. (b) Average experimental pressure–volume loops (solid lines) ± 1 SD (shaded area) for baseline, acute ischemia, and longitudinal patch. The loops show the rightward shift in volume caused by acute ischemia and subsequent leftward shift after longitudinal reinforcement. All experimental curves were generated by averaging raw data from a previous study by Fomovsky et al. [6]. (c) Normalized contractility loadcurves optimized for each finite element model to match the measured change in volume versus time curves. With fewer contracting elements, the acute ischemia and longitudinal patch models required higher normalized contractility compared to baseline. (d) Model pressure–volume loops for baseline, acute ischemia, and longitudinal patch. The simulated loops follow the experimental trends shown in panel (b).

We simulated full pressure–volume loops by applying the average pressure time course from each experimental case on the endocardial surface and optimizing the normalized contractility loadcurve $e(t)$ to match the measured time course of volume change relative to end diastole ($V(t)$ –EDV) for each experimental case. Because we only measured the pressure and volume

curves for one patch configuration (longitudinal reinforcement) in our previous experiments, for simulations where we compared different patch configurations we employed the acute ischemia pressure load and normalized contractility curves in our models of longitudinal, circumferential, and isotropic patch reinforcement.

Table 3 Comparison of optimized models to data

	Experiment	Model (range)	Error
EDV _{Baseline}	78.2 $\pm$ 15.5	78.79	0.001302
EDV _{Ischemia}	89 $\pm$ 18	88.33	0.001293
EDV _{Patch}	82.2 $\pm$ 16.2	82.48	0.001126
Remodeling $E_{\text{circ, ischemia}}$	0.095 $\pm$ 0.094	0.0621 (0.05895 to 0.06514)	0.01122
Remodeling $E_{\text{long, ischemia}}$	0.065 $\pm$ 0.045	0.05281 (0.04788 to 0.05842)	0.0065
Remodeling $E_{\text{circ, patch}}$	0.06 $\pm$ 0.1	0.0474 (0.0369 to 0.0558)	0.002387
Remodeling $E_{\text{long, patch}}$	−0.055 $\pm$ 0.071	−0.0477 (−0.0561 to −0.0369)	0.0004933
L _{BA}	4.256 $\pm$ 3.393	2.1053	0.07972
L _{SL}	2.827 $\pm$ 3.929	0.6273	0.04782
Total error			0.1519

Note: Italic values correspond to range for model results.

$$T(t, \lambda(t)) = e(t) \left[T_{\max} \frac{Ca_o^2}{Ca_o^2 + ECa_{50}^2(\lambda(t))} \right] \left[\frac{1 + aQ(t, \lambda(t))}{1 - Q(t, \lambda(t))} \right]$$

$$ECa_{50}(\lambda(t)) = \frac{Ca_{o\max}}{\sqrt{e^{\beta[\lambda(t)t_r - t_o]} - 1}} \quad (5)$$

$$Q(t, \lambda(t)) = A_1 \int_{-\infty}^t e^{-\alpha_1(t-\tau)} \dot{\lambda}(\tau) d\tau$$

$$\sigma_{\text{fiber, total}}(t, \lambda(t)) = \sigma_{\text{fiber, passive}}(\lambda(t)) + T(t, \lambda(t)) \quad (6)$$

Results

Optimized Models Match Measured Hemodynamics. Optimized passive material properties for the baseline, acute ischemia, and patch models are listed in Table 2 and optimized model outputs are shown relative to the data in Fig. 2 and Table 3. In order to capture the apparent softening of the acutely ischemic region, the isotropic (C_1), linear fiber (C_3), and exponential fiber (C_4) terms were reduced in the acutely ischemic myocardium by -50% , -30% , and -10% , respectively, relative to baseline. Following optimization of the normalized contractility loadcurves ($e(t)$ in Eq. (5)), model pressure–volume loops matched experimental data for all three conditions very well (Fig. 3). The optimized curves were quite similar for the ischemia and longitudinal patch cases (Fig. 3(c)), but both of these cases required substantially higher peak contractility than the baseline case to match measured volume changes.

End-diastolic and end-systolic pressure volume relationships (EDPVR and ESPVR, respectively) generated using the optimized FE models reproduced the major trends observed in the original experiment: ischemia shifted the ESPVR rightward and longitudinal patch reinforcement partially reversed that shift, with relatively little impact on diastolic properties (Fig. 4(a)). Comparing end-diastolic and end-systolic volumes at matched pressures, the FE models matched the experimentally measured changes due to acute ischemia and patch application closely (Fig. 4(b)).

Longitudinal Reinforcement Redistributes Fiber Stretch and Reduces Stress. Once we verified that the models matched the experimentally observed behavior during both acute ischemia and longitudinal reinforcement, we used the models to explore potential mechanisms underlying the functional benefit of longitudinal reinforcement. Plotting end-diastolic fiber stretch at matched pressures showed that ischemia increases stretch in the inner half of the wall (Fig. 5(a)), and longitudinal reinforcement partially relieves that endocardial stretch. Patch reinforcement also reduces end-systolic fiber stress in large portions of the noninfarcted myocardium relative to the acute ischemia simulation (Fig. 5(b)). Overall, the patterns of both end-diastolic fiber stretch and end-systolic fiber stress following patch reinforcement were similar to the baseline case, with the greatest stretch and active stress generation occurring deeper into the wall rather than directly on the endocardium as in the acute ischemia case.

Comparison of Different Patch Configurations. Given the many improvements in the current model relative to our previously published model of patch reinforcement [7], we decided to revisit the conclusion of that earlier paper that longitudinal reinforcement not only improves LV function but also does so to a greater degree than either circumferential or isotropic reinforcement. We therefore created two additional FE models of circumferential and isotropic reinforcement by using the same material properties for the patch layer but changing the fiber direction to be circumferential in all patch elements (circumferential) or radially symmetric about the center of the simulated infarct (isotropic). Comparing PV loops generated with identical pressure and normalized contractility loadcurves

confirmed that longitudinal reinforcement is most effective in reducing LV volumes (Fig. 6(a)), as well as in increasing stroke volume (Fig. 6(b)) relative to acute ischemia.

Plotting the change in end-systolic fiber stress relative to the acute ischemia case also showed that longitudinal reinforcement decreases fiber stresses throughout much of the LV, particularly in the inner half of the wall, while transferring some stress to the outer half of the wall (Fig. 7(a)). Isotropic reinforcement produces a similar pattern but smaller reductions in fiber stress, while circumferential reinforcement increases fiber stresses in most of the wall. These differences appear to result in part from shape changes induced by ischemia and reinforcement. In particular, ischemia increases the length (base–apex dimension) of the LV and longitudinal reinforcement restores this dimension to normal (Fig. 7(b)). Because we did not observe substantial changes to the septal–lateral or anterior–posterior dimensions with the different patch configurations (not shown), differences in their effects on the base–apex dimension led to a more spherical shape under longitudinal reinforcement and a more elliptical shape with

Fig. 4 Pressure–volume relationships: (a) EDPVR and ESPVR for experiments (symbols, data from Fomovsky et al. [6]) and model (lines), obtained by performing or simulating inferior vena cava occlusions. (b) Change from baseline in EDV at matched pressure of 12 mmHg (dEDV12) and end-systolic volume at 85 mmHg (dESV85) for acute ischemia and longitudinal patch. Experimental mean shown with open boxes $\pm$ 1SD and model simulations shown with filled boxes.

circumferential reinforcement (Fig. 7(c)). This effect on the geometry of the ventricle is also consistent with the increased stretch and contraction observed in circumferentially aligned fibers of the longitudinally reinforced model discussed above.

Discussion

The goal of this study was to construct a finite element model that could match our previously published data on changes in regional strains and left ventricular function following longitudinal surgical reinforcement of large anteroapical infarcts in dogs [6] and then use the model to explore potential mechanisms for the improvement in systolic function we observed. The model presented here, implemented in FEBIO, matches all the key features of our experiments, including diastolic remodeling strains in the ischemic region, small shifts in the EDPVR, and large changes in the ESPVR in response to ischemia and to patch application. Detailed examination of model strains and stresses suggests that longitudinal reinforcement reduces peak diastolic fiber stretch and systolic fiber stress in the remote myocardium and shifts those peaks away from the endocardial surface, in part by reshaping the LV.

The most interesting finding of our original experiment was that longitudinal reinforcement had no significant effect on the

end-diastolic behavior (as reflected in the EDPVR) but did shift the ESPVR leftward, increasing stroke volume under matched loading conditions (Fig. 4). Therefore, after building and validating the finite element model presented here, we next explored detailed plots of strains and stresses at both ED and ES. We found that while the end-diastolic pressures and volumes for the acute ischemia and patch-reinforcement models were fairly similar, patch reinforcement altered the ED transmural fiber stretch distribution more than we would have expected from the pressures and volumes alone. ED fiber stretch in the acute ischemia model was highest in the endocardial layer and higher than baseline throughout at least the inner half of the wall, even in regions far from the infarct. By comparison to ischemia, ED fiber stretch in the patch model was lower overall and especially at the endocardium; patch reinforcement transferred the region of highest stretch to the mid-wall, where the fibers are circumferentially aligned (Fig. 5). Plots of ES fiber stress showed very similar patterns, with the patch reducing high end-systolic stresses associated with acute ischemia throughout much of the left ventricular wall, particularly near the endocardium (Figs. 5 and 7). Based on these observations, we propose that longitudinal reinforcement improves systolic function primarily by reducing systolic fiber stress in the noninfarcted myocardium, allowing greater fiber shortening due to reduced

Fig. 5 Transmural stretch and stress distributions: (a) end-diastolic fiber stretch in the remote, noninfarcted elements of the baseline, acute ischemia, and longitudinal patch models seen in anterior-facing cross sections. Fiber stretch increases in the endocardial layer due to acute ischemia, but longitudinal reinforcement redistributes the increased fiber stretch to the midwall layer. (b) End-systolic fiber stress in the remote, noninfarcted elements of the baseline, acute ischemia, and longitudinal patch models seen in anterior-facing cross sections. Following a similar pattern to the end-diastolic stretch, acute ischemia leads to increased fiber stress in the endocardial layer, while longitudinal reinforcement leads to reduced fiber stress overall and a transmural redistribution that relieves the stress in the endocardium.

regional afterload. Shifting peak diastolic fiber stretch and active stress generation away from the endocardium toward the midwall may have the added advantage of engaging more circumferentially oriented fibers that have more leverage in generating LV pressure and shortening. Because the endocardium is normally the layer with the highest mechanical work and the lowest blood flow [19], *in vivo* this shift could also improve function by transferring more of the mechanical work to areas with the greater coronary perfusion reserve, an effect which is not captured in the model presented here.

Our model does not explicitly predict long-term effects of longitudinal reinforcement on left ventricular remodeling and the development of heart failure. However, in general, we would expect that acute improvements in pump function would reduce sympathetic activation and other compensatory reflexes known to drive the development of post-infarction heart failure. Based on current theories about how regional mechanics drive myocyte remodeling, we would also anticipate that decreasing peak end-diastolic fiber stretch would decrease the direct mechanical stimulus for eccentric hypertrophy that leads to dilation of the ventricle and contributes to heart failure.

Prior models have consistently predicted that isotropic reinforcement of acute infarcts would reduce both diastolic and systolic volumes without improving stroke volume and cardiac output [8,9]. We therefore performed a second set of simulations where we started with the fitted acute ischemia model presented here, held everything except material properties in the patch layer constant, and compared the effects of isotropic, circumferential, and longitudinal reinforcement (Figs. 6 and 7). These simulations showed that circumferential reinforcement produced the smallest predicted improvement in stroke volume and longitudinal reinforcement produced the largest, with isotropic reinforcement falling in the middle. These differences appeared to arise primarily through the effects of the different reinforcements on overall left ventricular shape. In the acute ischemia simulations, the large, relatively compliant anteroapical infarct caused the LV to take a more elliptical shape throughout the cycle. In contrast, the longitudinally reinforced model maintained a more spherical shape throughout the cycle, which enhances the increased fiber stretch in circumferentially aligned fibers. Interestingly, a more spherical shape is commonly associated with negative long-term outcomes [20–23], although the reasons for this are not completely understood. Longer-term simulations of growth and remodeling following each of these reinforcement cases could be an interesting follow-up to this study.

One novel feature of the model presented here is particularly important for informing future computational models of myocardial ischemia and infarction. Like most if not all prior models of acute ischemia, we have previously assumed that acutely ischemic myocardium has the same passive properties as normal myocardium but lacks the ability to generate active stress [7]. Using this approach, diastolic strains at a matched pressure are by definition identical at baseline and during ischemia, so remodeling strains computed between those states are always zero. Yet in our experiments, we found remodeling strains on the order of 10% during acute ischemia, and additional remodeling of similar magnitude after applying the patch. Because these strains are nearly as large as the strains associated with systolic shortening in normal myocardium and systolic bulging in ischemic myocardium, we would argue that any model wishing to accurately capture the effects of an intervention designed to alter regional mechanics in the infarct must first account for this diastolic remodeling.

One other detail of our approach may be of interest to other groups building finite element models of the heart. Rather than coupling our finite element model to a model of the circulatory system, we simulated *in vivo* loading conditions by applying measured LV pressure versus time curves to the model and iteratively adjusting a function that specified the time course of myocardial contractility ($e(t)$ in Eq. (5)) until the model matched measured LV volume versus time curves. This is conceptually

similar to the approach used by Guccione and coworkers [24,25] to estimate post-infarction regional contractility following infarction from regional strains. Stress generation in surviving myocardium might normally be expected to change following myocardial infarction due to sympathetic activation and related changes in calcium handling. However, our experimental data came from animals in which drugs were employed to block these responses. Thus, changes in regional stress generation in those animals could occur only through the Frank–Starling mechanism (increased force generation at longer sarcomere lengths). To the degree that our active contraction model accurately captures this length-dependent behavior, we should be able to fit pressure and volume data from the different runs with the same normalized contractility curve. This was only partially true in our simulations: the optimized contractility curves for the acute ischemia and longitudinal patch models were virtually identical, but peaked at a value of about 50% greater than in the baseline model (Fig. 3(c)). Given that EDP was lower at baseline, this may suggest that our active contraction model underestimates the magnitude of the Frank–Starling effect.

Our results may help to influence the design of new chronic reinforcement experiments, by identifying the design goal of redistributing transmural end-diastolic fiber stretch and maintaining an initially more spherical geometry. Our surgical approach to

Fig. 6 Simulations of different patch configurations: (a) pressure–volume loops for longitudinal, isotropic, and circumferential patch models, simulated using the same pressure loading and normalized contractility as the acute ischemia model. Baseline loop is shown for comparison. Longitudinal reinforcement leads to the greatest leftward shift in volumes compared to acute ischemia. (b) Corresponding percent change in stroke volume (EDV–ESV) relative to ischemia for model simulations of longitudinal (solid), isotropic (dotted), and circumferential (hatched) patch reinforcement. Longitudinal reinforcement leads to the greatest increase in stroke volume compared to acute ischemia.

Fig. 7 Stress and shape changes with different patch configurations: (a) longitudinal reinforcement decreases fiber stresses throughout much of the LV, particularly in the inner half of the wall, while transferring some stress to the outer half of the wall. Isotropic reinforcement produces a similar pattern but smaller reductions in fiber stress, while circumferential reinforcement increases fiber stresses in most of the wall. (b) Acute ischemia increases the base-apex dimension and longitudinal reinforcement restores this dimension to normal. (c) Longitudinal reinforcement leads to a more spherical shape throughout the cardiac cycle, while circumferential reinforcement produces a more elliptical shape.

longitudinal reinforcement ultimately failed in a chronic animal trial, because the functional benefits faded progressively as scar compaction unloaded the patch [10]. However, other localized strategies, such as injection or epicardial delivery of biomaterials, [26–31] might be adapted to produce selective longitudinal reinforcement, or achieve a similar redistribution of fiber stresses through alternate mechanisms.

Limitations

Despite the close match between the models presented here and the corresponding experimental data, several limitations of our models should be acknowledged. First, we captured the diastolic remodeling observed during acute ischemia by reducing the passive stiffness of the ischemic myocardium. However, the exact mechanism by which the ischemic region appears to soften is not well understood. Loss of pressurization of the coronary vessels may reduce passive stiffness directly [14], but loss of coronary perfusion also leads to an immediate thinning of the wall and thus higher stresses and stretches at matched EDP [13], an effect that was not explicitly modeled here. Our model also differed from the experiments in the way we simulated patch reinforcement. While in the experiments the patch was sewn on the surface of the infarcted region, in our model we defined the epicardial elements of this region as the patch material. Finally, our simulations of full cardiac cycles required optimizing distinct normalized contractility curves for each of our conditions in order to match the observed pressure–volume behavior. This approach is faster and simpler, but it is not as realistic as coupling the ventricular model to a model of the circulation [32]; as a result, the models

generated here will not necessarily produce physiologically plausible pressure–volume behavior when loaded with different pressure versus time curves.

Conclusion

In conclusion, we present here a new finite element model of local anisotropic reinforcement of the canine left ventricle acutely post-infarction. Our model captures both the local mechanics and global functional behavior in the average noninfarcted baseline, acutely ischemic, and patch-reinforced dog throughout the cardiac cycle. Our model shows that longitudinal reinforcement of the ischemic region reduces peak fiber stretch and stress in surviving myocardium and redistributes diastolic fiber stretch and systolic fiber stress transmurally. Longitudinal reinforcement and functional improvement result in part from a reshaping of the heart toward a more spherical geometry.

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Nomenclature

- a = force-velocity curvature parameter
- A_1 = slow tension weighting coefficient
- C_1 = passive isotropic parameter

C_3 = passive linear fiber parameter
 C_4 = passive exponential fiber parameter
 Ca_0 = initial calcium concentration
 Ca_{max} = maximum calcium concentration
 E_{circ} = circumferential remodeling strain
 E_{long} = longitudinal remodeling strain
EDP = end-diastolic pressure
EDV = end-diastolic volume
ESP = end-systolic pressure
ESV = end-systolic volume
EDPVR = end-diastolic pressure volume relationship
ESPVR = end-systolic pressure volume relationship
 K = bulk modulus
 l_{ref} = reference sarcomere length
 l_0 = unloaded sarcomere length
 L_{BA} = base to apex dimension
 L_{SL} = septal to lateral wall dimension
LV = left ventricle
MI = myocardial infarction
 T_{max} = maximum active tension
 α_1 = slow tension recovery rate constant
 β = length dependence active contraction parameter

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