MRI-based finite-element analysis of left ventricular aneurysm

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Previous FE studies of the LV have validated stress calculations by showing good agreement with myocardial deformations (strains) measured with implanted markers (5, 14, 29, 38, 39). However, this is invasive and is limited to few simultaneous LV locations (usually only 2). With advancements in magnetic resonance imaging (MRI), myocardial deformation can be quantified noninvasively throughout the LV with tagged MRI (8, 30). In a pioneering study, Moulton et al. (25) used tagged MRI to determine isotropic, diastolic material properties in a two-dimensional (2-D) FE analysis of beating canine hearts. Using a more realistic material law, Okamoto et al. (28) determined anisotropic myocardial material properties in a three-dimensional (3-D) FE model using tagged MRI. However, the experimental preparation and loading conditions were not physiological, to create significant transverse shear strain.

Since then, Guccione et al. (15) have successfully modeled end-isovolumic systole in an ovine model of MI and determined material parameters that reproduced circumferential stretching (as measured with 2-D tagged MRI) in the infarct border zone (BZ). This FE study successfully revealed that the mechanism of circumferential stretching in the infarct BZ during isovolumic systole related to impaired contractile function in that region. However, the FE model was validated against only two measurements of strain in the anterior and posterior BZ and lacked measurements of ovine material properties and fiber architecture.

The present study builds on these studies and uses tagged MRI to validate nonlinear, anisotropic, 3-D FE models in four sheep with MI. Moreover, this study incorporates ovine aneurysm material properties measured with biaxial stretching (24) and detailed helix angle measurements made with magnetic resonance diffusion tensor imaging (MR-DTI) in each heart (40).

METHODS

Animals used in this study were treated in compliance with the Guide for the Care and Use of Laboratory Animals, prepared by the Institute of Laboratory Animal Resources, National Research Council, and published by the National Academy Press, (revised 1996), and under approval of the Institutional Animal Care and Use Committee of the San Francisco Veterans Affairs Medical Center.

Myocardial Infarction

A previous study from our laboratory reported 3-D myocardial strains in an ovine infarct model at multiple time points after MI and...
ventricular restoration surgery (12). Animals 22 wk post-MI in the group with a sham operation (described below) were used for the present study. The infarct procedure has been described in detail previously (22). In brief, five adult sheep underwent anteroapical MI. Castrated male Dorsett sheep (40–50 kg) were anesthetized [ketamine 33 mg/kg im, isoflurane maintenance (2–4% inspired)] and mechanically ventilated (tidal volume 20 ml/kg; model 309-0612-800; Ohio Medical Products, Madison, WI). A left thoracotomy was performed using sterile technique, and the left anterior descending and second left anterior descending diagonal coronary arteries were ligated at a point 40% of the distance from the apex to the base as previously described (22). When present, branches of the posterior descending artery that also perfused this region were ligated 20% of the distance from the apex to the base. The thoracotomy was closed in layers, and the sheep recovered from anesthesia. Fifteen weeks later, these animals received a sham operation: a partial lower sternotomy was performed on the heart), the sternotomy was closed in layers, and the sheep recovered from anesthesia.

Experimental Measurements

After development of a large ventricular aneurysm (22.5 ± 1.5 wk post-MI), systolic strains were measured with tagged MRI as described in detail previously and summarized in this report (12). First, the sheep was intubated and anesthetized [1% inspired isoflurane (forane)]. A nonferromagnetic transducer-tipped pressure catheter (model SPC-320; Millar Instruments, Houston, TX) was introduced into the LV via sterile neck incisions. The animal was transported to the MRI scanner, and a series of tagged MR images were acquired in orthogonal short- and long-axis planes. Each image slice was synchronized to the R wave of the EKG signal, and sequential images were obtained at 40-ms intervals for the approximate completion of the cardiac cycle. Tagged MR images were transferred to a Silicon Graphics workstation (Mountain View, CA), the endocardium and epicardium were contoured, and tags were tracked semiautomatically (3). Systolic myocardial strains were calculated from tag-line deformation using the 4-D B-spline method (30) relative to cardiac coordinates (i.e., circumferential, longitudinal, and radial) at the midwall and around the circumference in each short-axis slice. These measurements have been reported previously (12).

To calculate LV volume, a 3-D surface was formed with a Delaunay triangulation of the endocardial contours in curvilinear coordinates in Matlab (The Mathworks, Natick, MA). LV volume was calculated by piecewise integration of the volume enclosed by this surface. Helix angle measurements were made postmortem using MR-DTI and have been reported previously (40).

FE Model

Computational 3-D (FE) models were created to replicate in vivo geometry at end-isovolumic relaxation by using both long- and short-axis slices (Fig. 1). LV volume was calculated for each time frame (every 40 ms) throughout systole, with the time frame with minimum LV volume taken to be end-isovolumic relaxation, and passive material laws were assumed to hold from this point. Endocardial and epicardial surfaces, formed as described above, were discretized into a finite element mesh containing 18 elements longitudinally, 12 elements circumferentially, and 1 element transmurally with linear interpolation in prolate spheroidal coordinates; the focal length was set to two-thirds of the distance from the base to the lowest endocardial point. Comparable to the method employed by Moustaki-dis et al. (27), aneurysm, remote, and BZ regions of the model were determined by ventricular wall thickness; the BZ region was defined at the steep transition in wall thickness between remote and aneurysm regions (Fig. 2).

Cardiac myofiber orientations from each heart were incorporated into the model. Ventricular geometries from tagged MRI and MR-DTI were reconciled by rotating and translating around a common LV axis to align the valves and right ventricular insertions. Alignment was further checked with markings of the asymmetric BZ in the two data sets.

After LV geometry was aligned, transmural samples of helix angles were taken from the MR-DTI data sets (10° wide and 5 mm tall at the epicardium, ~1,500 measurements in each transmural sample) from locations nearest each epicardial node on the FE model. A best-fit line was made to each transmural sample, and the epicardial and endocardial fiber angles were incorporated directly into the model. Unrealistic fiber angles, which occurred occasionally on the boundaries near the aneurysm or valves, were capped at an absolute value of 135° or set to average values of neighboring nodes. Fiber angles in the aneurysm were set to 0° to use experimentally determined aneurysm material parameters with respect to this direction (24).

In the FE model, fiber angles were defined in a local element coordinate system. To maintain the integrity of the helix angle measurements, the finite element mesh was formed using cylindrical-polar coordinates, thus keeping circumferential element lines perpen-

![Fig. 1. Building a finite-element (FE) model from in vivo MRI. Endocardial and epicardial contours from both short- (A) and long-axis views (B) are used to create the three-dimensional (3-D) FE model geometry (C). Tag deformation (A and B) is used to validate myocardial strain predictions from the FE model.](http://ajpheart.physiology.org/DownloadedFrom/10220334.9)
Fig. 2. Illustration of the border zone. A: border zone was defined at the steep transition of wall thickness between normal and aneurysm regions; color scale units are in mm. B: border zone elements in the FE model: blue, remote elements; red, border zone elements; green, aneurysm elements.

dicular to the ventricular axis. To capture the apical geometry, however, meshing in spherical-polar coordinates was required in the last six to eight longitudinal elements. The final geometry combined the cylindrical mesh and spherical cap in prolate-spheroid coordinates (Fig. 1C).

Boundary and Loading Conditions

Boundary constraints were applied in the same manner as described in previous models (6). Azimuthal displacements were constrained at all nodes at the base and apex during both filling and ejection. Circumferential displacement of the basal epicardial nodes also was constrained. End-systolic (ESP) and end-diastolic pressure (EDP) measured from the LV pressure catheter were offset by the minimum LV pressure (to compensate for not having an unloaded in vivo reference state) and applied to the endocardium of the FE model (Table 1).

Material Laws

The FE model is built on the laws of large deformation continuum mechanics and has been described previously (6, 15). In short, the passive myocardium was modeled by a strain energy function, \( W \), that is anisotropic relative to the local fiber direction:

\[
W = \frac{C}{2} (\epsilon^p - 1) \tag{1}
\]

where

\[
\epsilon^p = b_r E_{rr} + b_f (E_{ff} + E_{tt} + E_{ff} + E_{tt}) + b_{cr} (E_{rf} + E_{rt} + E_{fr} + E_{ft}). \tag{2}
\]

\( E_{rr} \) is strain in the fiber direction, \( E_{ff} \) is cross-fiber in-plane strain, \( E_{tt} \) is radial strain transverse to the fiber, and the remaining are associated shear strains. \( C, b_r, b_f, \) and \( b_{cr} \) are material parameters.

Active contraction was simulated by adding stress in the muscle fiber direction defined by a time-varying elastance model (15). For end systole, this reduced to the following equation:

\[
T_0 = \frac{T_{\text{max}}}{Ca_0^2 + ECa_{50}} C_i \tag{3}
\]

where \( T_{\text{max}} \) is the maximum isometric tension achieved at the longest sarcomere length and maximum peak intracellular calcium concentration \( (Ca_0)_{\text{max}} \):

\[
C_i = \frac{1}{2} (1 - \cos \omega), \quad \omega = \frac{0.25}{4} + \frac{t_f}{t_r}, \quad t_r = ml + b \tag{4}
\]

where \( m \) and \( b \) are constants. Length-dependent calcium sensitivity is given by

\[
ECa_{50} = \frac{(Ca_0)_{\text{max}}}{\exp[B(l - l_0)] - 1} \tag{5}
\]

where \( B \) is a constant, \( l_0 \) is the sarcomere length at which no active tension develops, and \( l_0 \) is the stress-free sarcomere length. Active material parameters were set to the following values as previously described (15): \( T_{\text{max}} = 135.7 \) kPa, \( Ca_0 = 4.35 \) μmol/l, \( (Ca_0)_{\text{max}} = 4.35 \) μmol/l, \( m = 1.0489 \) s/μm, \( b = -1.429 \) s, \( B = 4.75 \) μm⁻¹, and \( l_0 = 1.58 \) μm; \( l_0 \) is the sarcomere length in the unloaded configuration and was assumed to vary linearly from 1.78 μm at the endocardium to 1.91 μm at the epicardium in accordance with experimental observations of Rodriguez et al. (35).

The Second Piola-Kirchhoff stress tensor was defined as the sum of the passive and active stress components,

\[
S = \left( \frac{\partial W}{\partial \varepsilon} - pC^{-1} \right) + \mathbf{T} \tag{6}
\]

where \( C \) is the right Cauchy-Green deformation tensor, \( p \) is the

Table 1. Experimental volumes and pressures

<table>
<thead>
<tr>
<th>Animal</th>
<th>EDV, ml</th>
<th>ESV, ml</th>
<th>Stroke Volume</th>
<th>Ejection Fraction, %</th>
<th>Minimum, EDP, mmHg</th>
<th>ESP, mmHg</th>
<th>Offset EDP, mmHg</th>
<th>Offset ESP, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>S568</td>
<td>114.9</td>
<td>91.1</td>
<td>23.8</td>
<td>20.7</td>
<td>3.58</td>
<td>11.76</td>
<td>80.57</td>
<td>8.18</td>
</tr>
<tr>
<td>S269</td>
<td>105.4</td>
<td>68.4</td>
<td>37.0</td>
<td>35.1</td>
<td>13.29</td>
<td>20.20</td>
<td>78.48</td>
<td>6.91</td>
</tr>
<tr>
<td>S455</td>
<td>115.4</td>
<td>98.7</td>
<td>16.7</td>
<td>14.5</td>
<td>4.13</td>
<td>10.72</td>
<td>88.62</td>
<td>6.59</td>
</tr>
<tr>
<td>S574</td>
<td>96.0</td>
<td>80.4</td>
<td>15.6</td>
<td>16.3</td>
<td>2.47</td>
<td>8.53</td>
<td>90.90</td>
<td>6.06</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>107.9 ± 9.2</td>
<td>84.7 ± 13.2</td>
<td>23.3 ± 9.9</td>
<td>21.6 ± 9.4</td>
<td>5.9 ± 5.0</td>
<td>12.8 ± 5.1</td>
<td>84.6 ± 6.0</td>
<td>6.9 ± 0.9</td>
</tr>
</tbody>
</table>

EDV, end-diastolic volume; ESV, end-systolic volume; EDP, end-diastolic pressure; ESP, end-systolic pressure.
hydrostatic pressure variable enforcing incompressibility, \( \mathbf{F} \) is the Green-Lagrange strain tensor, and \( \mathbf{T} \) is a stress tensor comprising the active contracting stress. The Second Piola-Kirchhoff stress tensor was incorporated into the conservation law of continuum mechanics, which was then solved with the FE method over a curvilinear coordinate system (see Ref. 6 for further details).

Numerical integration was performed with \( 3 \times 3 \times 3 \) integration points per element. Previously published passive parameters for normal myocardium were used as initial values for the remote myocardium (14, 28, 29, 39). Material parameters determined from biaxial stretching experiments were used in the aneurysm (24). Because of a lack of experimental data of aneurysm tissue under shear loading, stretching experiments were used in the aneurysm (24). Because of a medium (14, 28, 29, 39). Material parameters determined from biaxial stretching experiments of Lin and Yin (21) and recent FE modeling results from Usyk et al. (38), simulations also were performed with an in-plane, cross-fiber stress equal to 40% of that along the muscle fiber direction.

**Determination of Material Parameters**

An iterative approach (illustrated in Fig. 3) was taken to determine appropriate material parameters that reproduce the measured in vivo ventricular volumes and myocardial strains. The FE model was first inflated to the measured offset EDP with initial material parameters taken from previously published studies summarized in Table 2 (14, 28, 29, 39) (note: in one of the later studies, converged values from an earlier model were used as initial material parameters); passive material parameter \( C \) from Eq. 1 was then scaled independently in the aneurysm and nonaneurysm regions to get the correct end-diastolic volume (EDV). Once the EDV was within a few percent (1.0 ± 1.1%), the model was further inflated to the measured offset ESP, and systolic contraction was simulated in the remote region; in the BZ, \( T_{\text{max}} \) from Eq. 3 was reduced by 50% in accordance with results from Okamoto et al. (28). Values for animal models (aneurysm \( 22.9 \pm 3.9\% \), BZ = 17.8 ± 1.3%, remote = 59.3 ± 3.0% of wall volume/mass). Final material parameters are listed in Table 3. Material parameters for animals S568, S455, and S574 were close to those determined previously by Okamoto et al. (28). Values for animal S269 converged closer to those from Omens et al. (rat) (29). An average of 24 ± 18 iterations per animal were required to complete the material optimization process.

Strain comparisons were very good and spanned all functional (remote, BZ, and aneurysm) and circumferential regions.

### Table 2. Material properties from previous studies

<table>
<thead>
<tr>
<th>Study</th>
<th>( C )</th>
<th>( b_c )</th>
<th>( b_t )</th>
<th>( b_b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okamoto et al. (28)</td>
<td>0.5123</td>
<td>67.0694</td>
<td>24.1558</td>
<td>21.60382</td>
</tr>
<tr>
<td>Vetter and McCulloch (39)</td>
<td>1.76</td>
<td>50</td>
<td>5</td>
<td>1.63</td>
</tr>
<tr>
<td>Omens et al. (29) (dog)</td>
<td>1.2</td>
<td>26.7</td>
<td>2</td>
<td>14.7</td>
</tr>
<tr>
<td>Omens et al. (29) (rat)</td>
<td>1.1</td>
<td>9.2</td>
<td>2</td>
<td>3.7</td>
</tr>
<tr>
<td>Guccione et al. (14)</td>
<td>0.88</td>
<td>18.5</td>
<td>3.58</td>
<td>1.63</td>
</tr>
</tbody>
</table>

\( C, b_c, b_t, \) and \( b_b \) are material parameters.

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**Statistical Analysis**

Stress values were taken from the central integration point of each element and weighted by the element volume. Four parameters were tested for statistical significance: active contraction material parameter \( T_{\text{max}} \), overall RMS error between model-predicted and measured strains, and weighted fiber and cross-fiber stress values (see Results). Statistical analysis was performed using paired \( t \)-tests with Bonferroni adjustments for multiple comparisons. All data are presented as means ± SD.

**RESULTS**

One study could not be analyzed because of uncorrectable imaging problems not discovered until postprocessing. The size of the aneurysm/infarct was highly reproducible among all the animal models (aneurysm = 22.9 ± 3.9%, BZ = 17.8 ± 1.3%, remote = 59.3 ± 3.0% of wall volume/mass). Final material parameters are listed in Table 3. Material parameters for animals S568, S455, and S574 were close to those determined previously by Okamoto et al. (28). Values for animal S269 converged closer to those from Omens et al. (rat) (29). An average of 24 ± 18 iterations per animal were required to complete the material optimization process.

Strain comparisons were very good and spanned all functional (remote, BZ, and aneurysm) and circumferential regions.
(anterior, posterior, lateral, and septal walls; 11 ± 3 short-axis slices, 630 ± 187 strain comparisons/animal). Figure 4 illustrates excellent agreement between circumferential strains measured with tagged MRI and those calculated with FE modeling in one animal (RMS error = 0.039). Notice the model agrees well with the measured experimental strains around the circumference and in the aneurysm, BZ, and remote regions (Fig. 4, A–C). Figure 5 illustrates RMS error between measured strains from tagged MRI and those predicted by the FE model. The addition of in-plane, active cross-fiber stress equal to 40% of that in the fiber direction improved strain agreement in every strain component (Fig. 5); compared with modeling myocyte contraction only in the direction of the muscle fibers, overall RMS error decreased by 27% (0.074 ± 0.016 to 0.054 ± 0.011, P < 0.05, Fig. 5).

End-systolic stress values are indicated in Fig. 6. Stress increased from the remote region to the BZ and was highest in the aneurysm. Fiber stress increased by 24% in the BZ relative to remote regions (24.2 ± 2.7 to 29.9 ± 2.4 kPa, P < 0.01). Cross-fiber stress showed even greater regional anisotropy, increasing by 115% in the BZ (5.5 ± 0.7 to 11.7 ± 1.3 kPa, P = 0.02). Radial stress was similar in all regions. Compared with normal stress components, shear stresses were negligible.

DISCUSSION

The present study details significant advancements in rigorously validated FE models of the LV after MI. This study includes four unique FE models customized with 1) detailed helical fiber angles measured with MR-DTI; 2) in vivo geometry measured with MRI; 3) aneurysm material properties measured with biaxial stretching; 4) in vivo volumes reproduced at measured, in vivo pressures; and 5) agreement to in vivo strains measured with tagged MRI throughout the LV. No previous biomechanical models of MI have been so rigorously validated: 630 ± 187 strain comparisons were made per animal, compared with 2 in the previous study (15). FE model strains show significantly better agreement with experimental measurements when active cross-fiber stress is added equal to 40% of that in the fiber direction. The better strain agreement with 40% active cross-fiber is in agreement with ex vivo biaxial stretching measurements made in barium-contracted myocardium by Lin and Yin (21) and with modeling results by Usyk et al. (38). These biomechanical findings represent a fundamental change in modeling active myocardial contraction; before these studies were performed, myocyte contraction was modeled only in the direction of the muscle fiber (5).

Lin and Yin (21) estimated that a large portion of the active cross-fiber stress can be attributed to fiber angle splay, as much as 30% of the stress in the fiber direction, but the remainder is due to an unknown mechanism. There is evidence that the contractile process itself can generate lateral forces (16). There also is evidence that the extracellular collagen network in the myocardium may contribute to cross-fiber stresses by tethering adjacent myocytes; Lamberts et al. (20) demonstrated these tethers to be important components in both diastolic and systolic function of the myocardium. The precise contribution of each of these components in the intact heart awaits future experiments.

Implications for LV Remodeling

In the BZ, our results show a 24% increase in midwall fiber stress relative to regions remote from the infarct and an even more dramatic 115% increase in cross-fiber stress. Jackson et al. (18) recently demonstrated in the ovine infarct model that normally perfused but hypocontractile BZ regions expanded over time. This phenomena is proposed to be a result of increased BZ stress leading to BZ apoptosis, fibrosis, and, ultimately, ventricular dysfunction (33). A plethora of experiments have demonstrated cascades of cellular responses in response to a stress or strain stimulus that could lead to this BZ extension (11). Of interest then is whether the biochemical responses are further amplified when simultaneously subjected to the high fiber and cross-fiber stresses calculated in this FE study. In addition, these stress calculations provide a benchmark to evaluate therapies aimed at reducing wall stress (2, 9, 37).

Comparison With Previous Work

In previous studies, Savage et al. (36a) computed wall stress in sheep models of MI using a closed form equation developed by Janz (19). Moustakidis et al. (27) also computed wall stress with a simplified FE approach. However, neither study accounted for different material properties in the aneurysm or fiber orientation in the remote and BZ regions. Our results suggest that midwall circumferential stress in the remote region is ~20% higher than in their reports, ~20% lower in the BZ, and ~140% lower in the aneurysm region (data from anterior wall in Table II in Ref. 39 and Fig. 4B in Ref. 28). Earlier, Bogen et al. (4) estimated stress using a spherical membrane model of LV aneurysm (LVA). They reported a 2.0 amplification of circumferential stress in the BZ after chronic infarction. Longitudinal stress in the BZ was not reported in the chronic infarct but was ~1.5 times that of remote regions after acute infarction (Fig. 9B in Ref. 4). Stress amplifications from our study were not as high (24% increase in fiber/circumferential...
Fig. 4. Circumferential strains showing excellent agreement between tagged MRI (A) and finite element calculations (B) from animal S568. C: detailed point-by-point comparison. Slice locations in C are indicated with magenta lines in A and B, with slice 1 the most basal. Notice the model predictions and experimental measurements agree in remote, border zone, and aneurysm regions (RMS = 0.039).
Changes from the pseudooptimized value. Results show that overall RMS error changed only slightly (±1.6%) within the two extremes. Moreover, EDV remained within ±0.7% and ESV changed by only ±2.3%. Thus the pseudooptimization procedure appears to be relatively insensitive to the degree of experimental variation in aneurysm material properties.

Uncertainty in strain measurements. A previous study showed an approximate ±0.03 uncertainty in estimating circumferential strains in the software package we used for strain calculations [approximately ±0.01 error from uncertainty in tag location plus 0.02 error from the method and software (see Fig. 7 and Table 3 in Ref. 7)]. This is close to the 0.028 ± 0.009 RMS error reported by Moulton et al. (26) using a comparable approach.

Uncertainty in stress predictions. To estimate how sensitive stress estimates are to errors in strain, $T_{\text{max}}$ was scaled in one model to vary average $E_{cc}$ within the range of its RMS error (±0.039). By doing so, average fiber stress changed by ±12.5% and cross-fiber stress by ±21.0%. However, the ESV also changed ±11.3 ml (±12.0%). We estimate the uncertainty in ESV to be ±3 ml after recalculation based on 0.5 mm uncertainty in contour location as reported by Bazille et al. (3). After $T_{\text{max}}$ was scaled to keep ESV within this uncertainty (±2.7 ml), fiber stress varied ±2.8% and cross-fiber stress ±4.7%. Thus we expect our fiber stress estimates to be accurate within ±3% and our cross-fiber stresses within ±5% when the model is bounded by both strain RMS error and ESV.

Limitations.

Although this study represents significant advancements in FE modeling of hearts with MI, it is not without its limitations. In particular, because of long computation times, a formal nonlinear optimization of material constants, which would require many iterations (28), was not feasible. If future software and hardware upgrades can decrease computation times significantly, a formal optimization following the modified Levenberg-Marquardt method employed by Okamoto et al. (28) would be a worthwhile pursuit; the manually directed pseudooptimization employed in this study lends itself directly to an objective function for such an optimization. Okamoto et al. successfully accomplished this formal optimization in passive myocardium. However, as indicated in METHODS, diastole...

![Fig. 5](image_url). RMS error between end-systolic strain measurements from tagged MRI and strain predictions from FE modeling. Error decreased in all strain components after the addition of active cross-fiber stress. $E_{cc}$, circumferential strain; $E_{ll}$, longitudinal strain; $E_{rr}$, and $E_{tt}$, shear strains.

![Fig. 6](image_url). End-systolic midwall stress values at the normalized afterload (78.8 mmHg). $T_{ll}$, fiber stress; $T_{cc}$, cross-fiber stress; $T_{rr}$, radial stress; $T_{21}$, $T_{31}$, and $T_{32}$, shear stresses. Fiber and cross-fiber midwall stresses were greatest in the aneurysm but were also elevated in the border zone relative to the remote region. Shear stresses were negligible.
represented only 10% of the total simulation time in the current study; the rest of the computation time was spent simulating systole. Furthermore, because of the long computation times, the FE models were only refined enough to give reasonable estimates at the midwall. Once again, software and hardware upgrades, currently being pursued in our laboratory, should decrease computation times and allow further refinement of the FE model.

A second limitation of this study is poor measurements of radial strain \( (E_r) \) from tagged MRI. This has been acknowledged by multiple researchers as a limitation of tagged MRI (7, 8). If a new method of postprocessing can accurately make these measurements, it would be valuable for the strain validation. Such a development is beyond the scope of this study, though.

Last, the FE method assumes an initial stress-free state, whereas obtaining such a state in the beating heart is difficult to obtain, especially when complicated with a dyskinetic aneurysm. The material constants used for the aneurysm were measured ex vivo relative to an unloaded state; this may explain the higher \( C \) values (Table 2) in the in vivo model relative to the experimental measurements. However, all previous in vivo FE simulations also had this limitation, and this stress-free limitation will remain in any clinical applications.

In summary, with the use of tagged MRI, MR-DTI, measured LV pressures, and in vivo geometry, experimental validation of FE models of LVA is far superior to anything done before. Moreover, this is accomplished in four different models. [Previously, the state of the art was only 1 model validated against only 2 measurements of strain (15), whereas in the present study, comparisons were made with >600 strain measurements in each model.] From this analysis, we have quantitatively established that significant active cross-fiber stress is necessary for accurate simulation of LV systole. In addition, we have shown that stress is elevated in both fiber and cross-fiber directions in the infarct BZ. With this rigorous evaluation of the pathological state, the effect of different therapies for LVA can be assessed. The developed methodology can be applied to analyze any treatment that affects LV geometry [e.g., infarct plication (10), patch repair (9), radio frequency heating (34)], changes in material properties such as synthetic gel injection (32) (with or without stem cells), or alters boundary conditions [e.g., the Acorn jacket (36), Myosplint (37), or passive patch restraint (23)]. Analysis of these therapies, by applying the same methodology as developed in this study, is currently being pursued in our laboratory. Furthermore, with the application of noninvasive MRI, the methodology is clinically feasible. Already in a pilot study, we have successfully implemented the methodology established in this study to determine material properties in a patient with diastolic heart failure. Ultimately, this study merges noninvasive tagged MRI and finite element analysis and brings LV mathematical modeling one step closer toward an ultimate goal of creating customized clinical evaluations and therapies.

GRANTS
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