Regional septal dysfunction in a three-dimensional computational model of focal myofiber disarray

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Usyk, T. P., J. H. Omens, and A. D. McCulloch. Regional septal dysfunction in a three-dimensional computational model of focal myofiber disarray. Am J Physiol Heart Circ Physiol 281: H506–H514, 2001.—MLC2v/ras transgenic mice display a phenotype characteristic of hypertrophic cardiomyopathy, with septal hypertrophy and focal myocyte disarray. Experimental measurements of septal wall mechanics in ras transgenic mice have previously shown that regions of myocyte disarray have reduced principal systolic shortening, torsional systolic shear, and sarcomere length. To investigate the mechanisms of this regional dysfunction, a three-dimensional prolate spheroidal finite-element model was used to simulate filling and ejection in the hypertrophied mouse left ventricle with septal disarray. Focally disarrayed septal myocardium was modeled by randomly distributed three-dimensional regions of altered material properties based on measured statistical distributions of muscle fiber angular dispersion. Material properties in disarrayed regions were modeled by decreased systolic anisotropy derived from increased fiber angle dispersion and decreased systolic tension development associated with reduced sarcomere lengths. Compared with measurements in ras transgenic mice, the model showed similar heterogeneity of septal systolic strain with the largest reductions in principal shortening and torsional shear in regions of greatest disarray. Average systolic principal shortening on the right ventricular septal surface of the model was −0.114 for normal regions and −0.065 for disarrayed regions; for torsional shear, these values were 0.047 and 0.019, respectively. These model results suggest that regional dysfunction in ras transgenic mice may be explained in part by the observed structural defects, including myofiber dispersion and reduced sarcomere length, which contributed about equally to predicted dysfunction in the disarrayed myocardium.

FOCAL MYOCYTE DISARRAY is a common structural abnormality observed in many cardiac diseases, including coronary heart disease, cor pulmonale, and dilated cardiomyopathy (23a). It is particularly prevalent in patients with hypertrophic cardiomyopathy (HCM), especially in the interventricular septum, which commonly displays greater hypertrophy than the free walls, with 25% or more of the wall disarrayed.

Because global ventricular performance can be apparently normal in HCM, regional measures of myocardial function have been sought. Kramer et al. (18) used magnetic resonance tissue tagging to measure the distributions of systolic segment shortening in patients with HCM. Compared with normal volunteers, circumferential and longitudinal shortening strains were more heterogeneous in the patient group, with the greatest depression in the septum. They concluded that this heterogeneity of regional function might reflect the regional distributions of myocardial disarray and fibrosis. In a similar study, also using tagged magnetic resonance imaging, Dong et al. (5) observed significantly decreased systolic wall thickening and circumferential shortening strain in HCM patients compared with normal patients, with the greatest impairment of segment function occurring in regions of the highest end-diastolic wall thickness.

While the presence of regional hypertrophy or disarray is associated with altered distributions of segment shortening, establishing a direct relationship between these structural abnormalities and altered myocardial mechanics has necessitated measurements of regional strain patterns in animal models. The MLV2v/ras transgenic mouse was found to display focal myofiber disarray and hypertrophy, predominantly in the septal wall (11). Karlon et al. (16) measured systolic septal wall strains and regional myofiber angle distributions in hearts from these mice and compared them with nontransgenic controls. Approximately 25% of the septal wall had disarrayed myocytes, as characterized by a statistical dispersion of local fiber orientation about the mean >20°. Mean fiber angles were also different in regions of disarray. Systolic principal shortening and torsional shear strains on the right surface of the septum were significantly lower in regions with underlying myocyte disarray than the strains in nondisarrayed regions. Systolic and diastolic sarcomere lengths were significantly shorter in disarrayed myocytes.

Although the study by Karlon and colleagues (16) showed for the first time that reduced systolic strains...
do coincide with the presence of focal alterations in myocardial tissue structure, it did not establish whether the measured structural defects were themselves directly responsible for the altered strain distributions. This does seem likely. A change in the mean orientation of myofibers in areas of disarray may alter local torsion because the transmural variation in fiber orientation contributes to the development of twist during systole. The increased angular deviation of disarrayed myofibers could also reduce tissue anisotropy, which is necessary for the development of systolic torsion (1). Lower sarcomere lengths suggest that myocytes in areas of disarray may operate at a lower point on their isometric length-tension curve, generating less systolic tension and shortening. To test these hypotheses and determine the relative importance of these potential mechanisms, we used three-dimensional computational models to investigate septal wall mechanics in normal and ras transgenic mouse left ventricles (LVs). Ventricular geometry and fiber architecture, including the presence of randomly distributed regions of disarray with shorter sarcomere lengths, were modeled based on the experimental measurements reported previously (13, 14).

Comparing model predictions with measured septal strain distributions showed that the loss of regional shortening and shear in disarrayed regions can be reasonably well explained by the observed focal defects in myocyte orientation and sarcomere length, with each mechanism contributing approximately equally to the observed loss of regional segment function.

**METHODS**

**Structural model.** Thick-walled ellipsoids were used to model the normal and hypertrophied mouse LV. Wall thicknesses were matched to the septal thicknesses in wild-type and ras transgenic mice as reported by Gottshall et al. (6) using M-mode echocardiography: 0.7 ± 0.0 mm for wild-type mice and 0.9 ± 0.1 mm for ras transgenic mice. The three-dimensional computational model with disarray was represented in prolate spheroidal coordinates (λ, M, and θ) using 1,024 trilinear finite elements and 1,360 nodes. Epicardial nodes at the base of the finite-element mesh were fixed in the circumferential (θ) and radial (λ) directions to simulate constraints imposed by the relatively stiff mitral valve annulus (7); the longitudinal coordinate (M) was fixed at all basal (M = 120°) and apical (M = 5°) nodes. Transmural mean fiber orientations were included in the model based on measurements made in control and ras transgenic mouse hearts (16), using linear interpolation of fiber angles between nodes. Sarcomere lengths in the unloaded reference state were included based on previous measurements (21).

**Passive mechanical properties.** Stress and strain in the LV were modeled using the finite-element method by passive filling to an end-diastolic pressure of 10 mmHg. An exponential form of the strain energy function has been previously used to model the resting myocardium (9, 23). The following form of the strain energy function (W) assumes that the material is hyperelastic, nearly incompressible, and orthotropic with respect to fiber and laminar sheet axes (4), consisting of the fiber axis Xf (along the myofibers), the sheet axis Xs (perpendicular to Xf and parallel to the sheet plane), and the sheet-normal axis Xn (perpendicular to the laminar sheet plane)

\[
W = C(e^q - 1)/2 + C_{\text{compl}}(J \ln J - J + 1)
\]

where

\[
Q = b_0 E_n^2 + b_a E_a^2 + b_m E_m^2 + b_d (E_d^2 + E_s^2) + b_b (E_b^2 + E_{al}^2) + b_m (E_m^2 + E_{cm}^2 + E_{cn}^2)
\]

where E_j are components of Green’s strain tensor E in an orthogonal coordinate system having fiber, sheet, and sheet-normal (f, s, n) axes, respectively; i and j = f, s, or n; and J is the determinant of the stretch tensor U. The values of the material constants (C_{\text{compl}} and b_j) have been previously estimated for models of passive ventricular mechanics (23, 24) and indicate that the normal passive myocardium is stiffer in the fiber direction than in the transverse direction, consistent with experimental measurements (19).

**Active contraction model.** Systolic contraction was modeled by defining the Cauchy stress tensor (T) referred to the local fiber coordinates as the sum of the passive three-dimensional stress tensor [T^{(p)}] derived from the strain energy function and an active stress tensor [T^{(a)}]

\[
T = T^{(p)} + T^{(a)}
\]

The components [T^{(a)}] of the active stress tensor were derived from the diagonal stress tensor (T^{active}) referred to fiber coordinates using a rotation matrix (q), which rotates a vector in the plane of the wall through a (deformed) fiber angle about the radial axis

\[
T^{(a)} = q^T T^{\text{active}} q
\]

The components of the active tensor T^{active} were a function of peak intracellular calcium concentration ([Ca^{2+}]_i) and sarcomere length. The formulation of the active model previously developed (8, 10, 12) was based on experimental measurements of sarcomere length-tension relations in rat trabeculae. The transverse components of the active stress tensor [T^{(a)}] were computed as a function of the fiber coordinate

\[
T^{(a)} = \text{max} (T^{(a)}_f, T^{(a)}_s, T^{(a)}_n)
\]

Disarray was modeled in the septal area [circumferential coordinate: Θ ∈ [0°, 180°]; longitudinal coordinate: M ∈ [30°, 110°)] by separate groups of finite elements. The pattern of disarray was reconstructed from the regional distributions of disarray observed by Karlon et al. (16), who measured local fiber orientation and angular deviation in 21 × 21 grids from each of nine transmural tissue sections spaced equally through the septal wall thickness. With the use of these original data, we calculated, for each heart, the number of disarrayed three-dimensional regions and the distribution of their volumes in seven mice. On the basis of these statistics, we built a stochastic region-growing algorithm to generate random three-dimensional regions of focal disarray in the model, occupying ~25% of the finite elements (100 elements) in the septal wall of the model (see Fig. 1 and RESULTS). Each finite element in the septal wall of the model was assumed to be either entirely normal or entirely disarrayed (piecewise constant variation). The steps in generating a region-growing algorithm are as follows: 1) Randomly select the first element of region k by coordinates X_i(1), where i = 1 . . . 3 and X_l(1) = 1 . . . X_i(\text{max}). 2) If k > 1 and this element already exists or is connected with an existing region, then repeat step 1. 3) Randomly select the direction of growth and, using

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2. each mechanism contributing approximately equally to in myocyte orientation and sarcomere length, with reasonably well explained by the observed focal defects shortening and shear in disarrayed regions can be
3. modeled based on the experimental measurements reported previously (13, 14).
4. Comparing model predictions with measured septal strain distributions showed that the loss of regional shortening and shear in disarrayed regions can be reasonably well explained by the observed focal defects in myocyte orientation and sarcomere length, with each mechanism contributing approximately equally to the observed loss of regional segment function.
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nally by altering material properties in the finite-element model.

Mechanism 1: increase in myofiber AD. Dispersion of fiber orientation was measured by Karlton et al. (16) as the local AD (angular equivalent of standard deviation) of myofiber orientation. To determine the net contribution of a family of myofibers with a known distribution of orientations, a superposition of local stress contributions was performed. Fiber, sheet, and sheet-normal stresses acting along the mean myofiber, sheet, and sheet-normal axes in an ensemble of cells is obtained by integrating myofibril tractions over the distribution of myofiber angles $\mathbf{f}(\theta)$

$$
\mathbf{T}_{\text{active}} = \int_{\mu} \int_{\theta} (\mathbf{Q} \mathbf{T}_{\text{local}}^\mathrm{fiber} \mathbf{Q}^T) \times \mathbf{f}(\theta) \times \varphi(\mu) \, d\mu \, d\theta
$$

where $\mathbf{T}_{\text{local}}^\mathrm{fiber}$ is a function of peak $[\mathrm{Ca}^{2+}]$, and sarcomere length; $\mathbf{T}_{\text{active}}^\mathrm{fiber}$ and $\mathbf{T}_{\text{active}}^\mathrm{sheet}$ are constant fractions ($k$) of the active fiber stress $\mathbf{T}_{\text{active}}^\mathrm{fiber}$ (23); $\theta$ and $\mu$ are angles that describe the relationship between the local myofiber axis and the mean fiber axis; $\mathbf{f}(\theta)$ is the fiber orientation probability density distribution, which can be described using a von Mises distribution; $\varphi(\mu)$ is also density distribution, which can be described as $\varphi(\mu) = 1/(2\pi) |\mu| (\mu \in [1;2\pi])$; and the rotation matrix $\mathbf{Q}$ defines the relation between the mean fiber-sheet coordinate system ($\mathbf{X}_{\text{fiber-sheet}}$) and local cell coordinate system ($\mathbf{X}_{\text{local}}$).

$$
\mathbf{X}_{\text{fiber-sheet}} = \mathbf{Q} \mathbf{X}_{\text{local}}
$$

$$
\mathbf{f}(\theta) = f^\mathrm{v}(\theta) \begin{bmatrix} 1 & 0 & 0 \\ 0 & \lambda / \lambda_f & 0 \\ 0 & 0 & \lambda / \lambda_f \end{bmatrix} = f^\mathrm{v}(\theta) \mathbf{\Lambda}
$$

where $f^\mathrm{v}(\theta)$ is the fiber orientation probability density in the undeformed reference state and $\lambda$, are fiber, sheet, and normal-sheet extensions. The function $f^\mathrm{v}(\theta)$ may also depend on the angle $\mu$.

We can rewrite the equation for $\mathbf{T}_{\text{active}}$ as follows

$$
\mathbf{T}_{\text{active}} = \frac{1}{2\pi} \int_{\mu} \int_{\theta} (\mathbf{Q} \mathbf{T}_{\text{local}}^\mathrm{fiber} \mathbf{Q}^T) f^\mathrm{v}(\theta) \, d\mu \, d\theta \cdot \mathbf{\Lambda}
$$

After integration, we have

$$
\mathbf{T}_{\text{active}} = \begin{bmatrix} \mathbf{T}_{\text{active}}^{\text{fiber}} & 0 \\ 0 & \mathbf{T}_{\text{active}}^{\text{sheet}} \\ 0 & 0 & \mathbf{T}_{\text{active}}^{\text{sheet-normal}} \end{bmatrix}
$$

With the use of these equations, with a measured average AD of 12° for normal myocardium and 25° for disarrayed tissue, we obtained a ratio of systolic cross-fiber to fiber stress of 0.452 in normal muscle versus 0.697 in disarrayed elements.

Mechanism 2: reduction in sarcomere length. Development of systolic tension in cardiac myocytes is dependent on activator calcium concentration and sarcomere length (22A). The isometric length-tension curve describes the tension development at different sarcomere lengths for given concentrations of calcium. This suggests that these myocytes operate at a lower point of the sarcomere length-tension curve, thus generating less tension and shortening. Systolic isometric fiber stress development in the model was computed as a function of activator calcium concentration and sarcomere length according to the model of length-dependent activation by Gucione et al. (9).

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**Fig. 1.** Fiber orientation and disarray location for the left ventricular (LV) endocardial surface (A) and right side of the septum (B).
Areas of disarray were modeled with sarcomere lengths measured in the reference state (13). Briefly, groups of ras transgenic \( n = 6 \) and control hearts \( n = 7 \) were fixed at zero pressure and under barium contracture as a model of end systole. The tissue was embedded in plastic, sectioned at a thickness of 5 \( \mu \text{m} \), and stained with toluidine blue. Sarcomere lengths were found at \( \times 1,000 \) magnification by measuring 10 adjacent sarcomere lengths in at least 10 random locations in any given section. Measurements were made at subepicardial (\(-15–25\% \) depth), midwall (\(45–55\% \) depth), and subendocardial (\(75–85\% \) depth) regions. Measurements were made in five sections from each depth each with a different knife angle. The smallest average sarcomere length was used from each depth because off-angle sectioning resulted in overestimation of the measurements. Sarcomere lengths were significantly smaller in areas of myofiber disarray compared with areas of normally arrayed tissue in ras transgenic mouse hearts and compared with control hearts in both the zero-pressure and barium contracture states. There was no significant difference between the control group of hearts and areas of normally arrayed tissue in ras transgenic mouse hearts at either loading state. No significant variation with wall depth was found in sarcomere length at either zero-pressure or under barium contracture in either group of animals. Thus we used the measured midseptal values for average resting sarcomere length in the model (2.00 \( \mu \text{m} \) for control and 1.65 \( \mu \text{m} \) for disarray).

### RESULTS

**Biaxial model of disarrayed tissue.** The biaxial contraction of orthotropic cubes with material properties of normal cardiac muscle or disarrayed myocardium was simulated. Figure 2 shows stress-strain curves in fiber and cross-fiber directions for normal tissue and disarrayed tissue. The influence of reduced sarcomere length and myofiber AD are also shown separately. These results illustrate the significant effects of disarray on myocardial systolic mechanical properties.

**LV model of a wild-type mouse heart.** Figure 3 compares model results with experimentally measured data (14) for the principal strains \( E_1 \) and \( E_2 \) and the torsional shear \( E_{12} \) on the RV surface of the septum in the wild-type mouse heart. Computed strain components for the LV surface of the septum are also shown. On the RV surface of the septum, the model showed good agreement with measurements of \( E_1 \) and \( E_{12} \) but poorer agreement for \( E_2 \).

**Effect of septal wall hypertrophy.** Figure 4 shows strain components computed with the hypertrophied but not disarrayed LV model normalized to the corresponding strains found in model of the wild-type mouse heart. There was an increase in the septal in-plane shear \( E_{12} \), especially on the RV surface, and a decrease in the second principal strain \( E_2 \). The major principal strain \( E_1 \) did not change significantly. These effects of hypertrophy are consistent with calculated results for

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**Fig. 2.** Systolic stress-strain curves for normal and disarrayed tissue in biaxial deformation of an orthotropic cube. The influence of sarcomere length (SL), angular dispersion (AD), and both of these factors together \((SL + AD)\) are shown. A: fiber stress-strain relations. B: cross-fiber stress-strain relations.

**Fig. 4.** Average strain for model of hypertrophied mouse LV normalized to strains found in the wild-type mouse model. First principal strain \( E_1 \), second principal strain \( E_2 \), and torsional shear \( E_{12} \) found on the RV surface and the LV surface of the septum are shown.
a two-dimensional model (14) and previous experimental investigations (11).

Spatial distribution of disarray. Table 1 shows average values for the number and fractional volume of three-dimensional disarrayed regions reconstructed from the original histological measurements (16). The locations of septal disarray areas showed no consistent pattern between individuals. It can be seen from this statistical analysis that the disarrayed myocardium typically consisted of one large region with a complicated geometry and several smaller regions. With the use of these statistics on the number and size of three-dimensional disarrayed regions, a random region-growing algorithm was used to generate the pattern of disarray used in the model. Table 1 compares the summary statistics of the modeled distribution of disarray with those computed from the original histological measurements.

Wall thickening. Wall thickening at end systole referenced to end diastole was calculated for the normal, hypertrophic, and disarrayed hypertrophic walls. The hypertrophied wall was thicker at end diastole, but the percent wall thickening was reduced from 41.0% to 29.6%. The change in fiber orientation produced a reduction in wall thickening, whereas addition of cross-fiber tension produced an increase in wall thickening. Change in sarcomere length or a combination of all mechanisms produced only a small reduction in wall thickening.

Strain and stress components. Maps of the three-dimensional principal strain components $E_1$ and $E_2$ and shear strain $E_{12}$ for a realistic distribution of disarray are shown for the right side of the septum and the subendocardial surface in Fig. 5. The area shown is

<table>
<thead>
<tr>
<th>Volume of Each Disarrayed Region Normalized to Septal Volume</th>
<th>Average Number of Regions</th>
<th>Average Volume of All Regions Within Current Size Normalized to Septal Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume observed</td>
<td>Experimental Observations</td>
<td>Model</td>
</tr>
<tr>
<td>0.00025–0.0025</td>
<td>9 ± 5.0</td>
<td>0.0065 ± 0.0043</td>
</tr>
<tr>
<td>0.0025–0.0075</td>
<td>2 ± 1.0</td>
<td>0.0055 ± 0.0059</td>
</tr>
<tr>
<td>0.0075–0.0250</td>
<td>1 ± 0.0</td>
<td>0.0116 ± 0.0138</td>
</tr>
<tr>
<td>&gt;0.0250</td>
<td>1 ± 0.0</td>
<td>0.2119 ± 0.1171</td>
</tr>
<tr>
<td>Sum</td>
<td>13 ± 6</td>
<td>0.2355 ± 0.1411</td>
</tr>
</tbody>
</table>

Values are means ± SE.
similar to the area where nonhomogeneous strains were measured in isolated heart experiments (14). The maximum principal strain $E_1$ was most sensitive to the presence of disarray, similar to a previous experimental finding (15). There was a local increase in the magnitude of $E_1$ associated with the increase in AD. The influence of disarray on the strain components $E_1$ and $E_{12}$ was more significant at the right side of the septum than the LV subendocardium (left side). Conversely, for the minimal principal strain component $E_2$, the influence of disarray was greater on the left and less on the right side. A map of principal stress components $T_1$ and $T_2$ for the right and left side of the septum (Fig. 6) shows that the effect of disarray was greater on $T_1$ than on $T_2$.

Average correlation coefficients were calculated to compare the local RV septal surface strain with local AD values from four tissue sections (in the middle of each finite element). The positive correlation coefficient of $E_1$ indicates a relationship between increased AD and more positive $E_1$ (reduced shortening). The correlation coefficient was significantly greater for the section closest to the RV septal surface, indicating a closer spatial relationship between disarray and septal surface dysfunction. There was a trend toward more negative correlation near the RV septal surface and positive correlation at the LV septal surface. Because $E_2$ was generally negative in sign, with positive correlation near the LV septal surface, this indicates that greater AD (increased disarray) is more likely to be associated with more positive $E_2$. Both these results indicate that the surface strain is reduced in areas of disarray, and both agree qualitatively with our earlier experimental investigations (14).

Average principal strains on the RV and LV septal surfaces corresponding to areas of disarray are shown in Fig. 7. There was a significantly reduced average systolic strain associated with disarrayed tissue found near the RV septal surface. The subendocardial systolic strains associated with disarrayed tissue found near the LV side of the septal wall were less reduced. The average surface strains $E_2$ and $E_{12}$ for areas of disarray are also shown in Fig. 7. There were significantly smaller average RV surface shear strains $E_{12}$ and principal strains $E_2$, associated with areas of disarrayed tissue near the RV septal surface. Near the LV septal surface, torsional shear was increased compared with the model of hypertrophy. The effects of reduced sarcomere length and reduced anisotropy are separately shown in Fig. 7 for principal strains $E_1$ and $E_2$ and shear strain $E_{12}$. The contribution of reduced sarcomere lengths was similar to that of decreased anisotropy for strains $E_1$ and $E_{12}$ but different for $E_2$ (see Fig. 7).

Figure 8 shows average values of the RV septal surface for $E_1$ and $E_{12}$, associated with areas of the wall that are affected by various amounts of disarray normalized to corresponding strain solutions from the

Fig. 6. Maps of principal stresses $T_1$ and $T_2$ for the LV endocardial surface (A) and right surface of the septum (B).
model of the wild-type mouse heart. Areas with more dense disarray were associated with smaller RV septal surface shear strain $E_{12}$, similar to the experimental results (16), but the observed differences were greater (see Fig. 8). Maximum and minimum principal systolic shortening ($E_1$ and $E_2$) in more densely disarrayed areas were smaller than those in less dense areas, but these variations were less significant than for the torsional systolic shear strain $E_{12}$.

DISCUSSION

We used a numerical model to test the hypothesis that focal changes in the microstructural properties of the disarrayed myocardium are directly responsible for the patterns of regional dysfunction that were recently measured on the septal surface of the MLC2v/ras transgenic mouse heart (16). We investigated the influence of three different structural properties of disarrayed myocardium using a three-dimensional finite-element model of systolic contraction. Models were created of the normal and hypertrophied ventricle based on previously published measurements made on the transgenic mouse with ventricular expression of ras, which displays morphological characteristics of HCM (11). A realistic three-dimensional distribution of disarray affecting ~25% of the wall was used to match the experimental measures.

The model of the wild-type mouse heart did not agree especially well with experimental measurements, especially for the second principal strain (see Fig. 3). This may be because, for the present study, a simple ventricular geometry was used and material properties were assumed to be transversely isotropic, neglecting the possible effects of myocardial laminar sheet structure. The coefficients of the constitutive law were chosen from previous studies (23, 24) in other species, which may not be representative of the mouse heart, especially under conditions of hypertrophy and disarray. Indeed, focal fibrosis is commonly observed to accompany myocyte disarray in animals and humans and was observed in the ras transgenic mouse. This may increase regional diastolic muscle stiffness and possibly effect systolic mechanics as well. We examined the sensitivity of the model results to passive material parameters by repeating the analysis with a different set of constitutive parameters derived from recent experiments in mice. The following material parameters of a transversely isotropic incompressible constitutive equation were estimated from uniaxial tests in passive murine papillary muscles and isolated ventricles: $C_1 =$

Fig. 7. Average strains on the RV surface and LV surface of the septum normalized to strains for the hypertrophied mouse model. First principal strain $E_1$, second principal strain $E_2$, and torsional shear $E_{12}$ in areas with disarray found at the subepicardium (RV) or subendocardium (LV) are shown. The influence of SL, AD, and both of these factors together (SL + AD) in the model are shown.

Fig. 8. Average strains on the RV surface of the septum normalized to strains found in the wild-type mouse model. First principal strain $E_1$ and torsional shear $E_{12}$ associated with varying amounts of septal wall disarray for the model and experimental observations (14) are shown.
The influence of decreased anisotropy and reduced sarcomere length were almost the same on the maximal principal shortening and torsional strain but different for the minimum principal shortening. Because the experimental studies showed no significant changes in $E_2$, we focused our comparisons primarily on the other strain components. A combination of all characteristics of the disarranged myocardium resulted in the greatest effect on strain and the best agreement between model and experimental observations.

The greatest effect of myofiber disarray on experimental epicardial function was found for the maximum principal strain $E_1$ and torsional shear (15). This finding was also duplicated in the present finite-element modeling study. It has been suggested by Lin and Yin (19) that the dispersion of fibers in the normal myocardium may be at least partly responsible for the development of substantial cross-fiber systolic stress. Bonvendeerd et al. (3) showed that myofiber imbrication angle causes local variation in strain magnitudes in a model of the LV. These investigations highlight the importance of myofiber dispersion in regional mechanics. Imbrication angle was not included in our analysis but is typically $5^\circ$.

More extensive disarray had a greater influence on epicardial strain than less extensive disarray. Additionally, this result indicates that disarray that affects a greater percentage of the wall thickness has the greatest effect on strain. This finding is also consistent with experimental results (14) showing that when a greater percentage of the wall thickness was affected by disarray, there was a greater reduction in RV surface strain components. The differences in strain components between the model and experimental observations for the same amounts of disarray were most significant for the shear strain (see Fig. 8). The change in material properties between disarrayed and nondisarrayed tissue was modeled sharply from element to element, which is unlikely to approximate the transition in real tissue and might be one explanation for the differences between numerical and experimental results. This may also explain why the torsional shears for the nondisarrayed tissue were greater than those in the model of the wild-type mouse heart, which also disagrees with the experimental findings.

Experimental evidence from magnetic resonance imaging studies on human HCM is inconclusive, with some investigators finding a decrease in wall thickening associated with the hypertrophic septum (5) but others finding no change (26). Echocardiographic studies on the ras transgenic mouse model did not show evidence of alteration in wall thickening (11).

This finite-element study indicates that multiple mechanisms may be responsible for the dysfunction associated with myofiber disarray and may be associated with diseases such as familial HCM. The findings from the finite-element model are qualitatively similar to those found in experimental studies. We conclude that decreased fiber tension associated with increased AD and reduced sarcomere length contribute approxi-
mately equally to the dysfunction in disarrayed regions.

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