Effects of Undersized Mitral Annuloplasty on Regional Transmural Left Ventricular Wall Strains and Wall Thickening Mechanisms

Allen Cheng, MD; Tom C. Nguyen, MD; Marcin Malinowski, MD; David Liang, MD, PhD; George T. Daughters, MS; Neil B. Ingels Jr, PhD; D. Craig Miller, MD

Background—Undersized mitral annuloplasty, widely used for ischemic and functional mitral regurgitation (MR), has been proposed as an “annular solution to a ventricular problem.” Beyond relief of MR, it is thought to improve global left ventricular (LV) shape, hence potentially reducing myocardial stress and promoting beneficial reverse LV remodeling. We previously observed that undersized annuloplasty inhibited systolic wall thickening at the LV base near the mitral annulus. In this study, we measured the effects of undersized annuloplasty on regional transmural LV wall fiber and sheet strains and wall thickening mechanisms.

Methods and Results—Nine sheep had transmural radiopaque beadsets surgically inserted into anterobasal and lateral equatorial LV regions, with additional markers silhouetting the LV and mitral annulus. 4-Dimensional marker dynamics were studied with biplane videofluoroscopy before and after tightening an adjustable Paneth-type mitral annuloplasty suture. Transmural circumferential, longitudinal, and radial systolic and remodeling strains in the subepicardium (20% depth), midwall (50%), and subendocardium (80%) in both regions were computed. Fiber and sheet angles from quantitative regional histology allowed transformation of these strains into local fiber (f), sheet (s), and sheet-normal (n) coordinates. Further analysis calculated the transmural contributions of sheet extension ($E_{sn}$), sheet thickening ($E_{nnc}$), and sheet shear ($E_{sns}$) to systolic wall thickening ($E_{33}$). In the anterobasal region, undersized annuloplasty reduced systolic wall thickening ($E_{33}$) by $\approx$50% at all transmural depths by inhibiting: (1) subendocardial systolic fiber shortening ($-0.10\pm0.05$ versus $-0.04\pm0.05$; $P<0.05$); (2) subepicardial (0.16±0.15 versus 0.09±0.08; $P<0.05$) and subendocardial (0.45±0.40 versus 0.19±0.18; $P<0.05$) systolic sheet thickening; (3) midwall sheet extension (0.22±0.12 versus 0.11±0.06; $P<0.05$); and (4) transmural sheet shear (subepicardium, $-0.14\pm0.07$ versus $-0.08\pm0.07$; midwall, 0.21±0.12 versus 0.10±0.11; subendocardium, $-0.19\pm0.23$ versus $-0.11\pm0.16$; $P<0.05$). In the remote lateral equatorial region, fiber-sheet strains and $E_{33}$ were unchanged.

Conclusions—In this acute animal study, undersized annuloplasty inhibited systolic wall thickening in the anterobasal region by reducing subendocardial systolic fiber shortening and laminar sheet wall thickening, but had no effects in a more distant LV region. This suggests that undersized mitral annuloplasty may have potentially deleterious effects on local myocardial mechanics. (Circulation. 2006;114[suppl I]:I-600–I-609.)

Key Words: congestive heart failure ■ fiber and sheet strains ■ LV myocardial normal and shear strains ■ LV wall thickening ■ mitral annuloplasty ■ systolic function

Undersized mitral ring annuloplasty, or the Bolling procedure, has been proposed as an annular solution to a ventricular problem in patients with ischemic (IMR) or functional mitral regurgitation (FMR). In addition to minimizing mitral regurgitation, it is postulated that this procedure normalizes left ventricular (LV) shape (more elliptical) and therefore may potentially reduce myocardial stress and promote reverse LV remodeling. In a previous analysis of undersized annuloplasty effects on LV myocardial cardiac strains, we observed that undersized annuloplasty increased LV wall thickness at end-diastole (ED) near the annulus in the anterobasal LV wall, whereas end-systolic (ES) wall thickness was unchanged such that systolic radial wall thickening was reduced in all transmural depths. The direct effects of undersized annuloplasty on transmural LV fiber and laminar sheet strains in different LV regions, however, are unknown. The objective of this study was to assess the effects of undersized annuloplasty on regional transmural LV wall fiber

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I-600
and sheet strains and wall thickening mechanisms in normal sheep hearts.

**Methods**

All animals received humane care in compliance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the Guide for Care and Use of Laboratory Animals prepared by the National Academy of Sciences and published by the National Institutes of Health (DHHS NIH publication 85-23, revised 1985). This study was approved by the Stanford Medical Center Laboratory Research Animal Review Committee and conducted according to Stanford University policy. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

**Surgical Preparation and Marker Data Acquisition**

The surgical preparation and marker data acquisition methods for these experiments have previously been described in detail. Briefly, 13 subepicardial radiopaque markers surgically implanted in nine sheep hearts to silhouette the left ventricle (Figure 1). Epicardial echocardiography was used to locate and measure the thickness of the mid-lateral equatorial LV wall between the papillary muscles and another site in the anterobasal LV wall basal to the insertion site of the anterolateral papillary muscle. Three transmural columns of beads (4 beads per column, Figure 1) were implanted into each region using a bead insertion apparatus oriented normal to the local epicardial tangent plane. On cardiopulmonary bypass (CPB), 8 radiopaque markers were implanted around the mitral annulus and 1 marker at each of the mitral leaflet edges (Figure 1). A modified Paneth-Burr annuloplasty suture was then inserted using a double-armed 2-0 polypropylene suture anchored at the left fibrous trigone, suturing around the anterior commissure in the annulus with pledgets, and exteriorized at the mid-lateral annulus using a tourniquet on the epicardial surface. A similar suture starting at the right fibrous trigone around the posterior commissure was placed in the ventricle through the apex. Immediately postoperatively, each animal was transferred to the cardiac catheterization laboratory and studied under open-chest conditions, intubated, mechanically ventilated, and anesthetized with isoflurane (1% to 2.5%). With the heart in normal sinus rhythm and ventilation transiently arrested at end-expiration, simultaneous biplane videofluoroscopic images (60 Hz), ECG, and LV and aortic pressures were recorded during steady-state baseline conditions before (control) and after tightening of both annular sutures. Tightening of the suture annuloplasty (~4 to 5 mm) in all animals was performed by the same investigator (A.C.). Transesophageal echocardiography was used to monitor flow across the mitral valve and no mitral stenosis or significant changes in gradients across the mitral valve were noted after suture annuloplasty tightening. Marker coordinates from the 2 radiographic views were digitized and merged to yield 3-dimensional (3-D) coordinates for each radiopaque marker and bead frame-by-frame (ie, every 16.7 ms). At the end of the study, 3.0-mm coronary perfusion balloon catheters (GUIDANT AguilTrac Peripheral Catheter; Santa Clara, Calif) were placed into the proximal circumflex and left anterior descending coronary arteries, and the animal was euthanized using sodium pentothal (1 gram intravenous) followed by an intravenous bolus of potassium chloride (80 mEq) to arrest the hearts at ED. After adjusting left ventricular pressure by blood withdrawal to match the previous in vivo LV end-diastolic pressure, buffered glutaraldehyde (5%, 300 mL) was infused simultaneously into both coronary arteries to fix the hearts in situ. All hearts were then explanted and stored in 10% formalin for later histological examination.

**Quantitative Histology**

The quantitative histological methods have been previously described in detail. Briefly, a transmural rectangular block of myocardial tissue, directly contiguous and basal to the implanted marker columns (Figure 2), was removed from the ventricular wall in each region studied, with the edges of the block cut parallel to the local LV circumferential (X₁), longitudinal (X₂), and radial (X₃) axes. After recording the overall transmural thickness of the specimen, the tissue block was sliced into 1-mm-thick sections parallel to the X₁-X₃ plane and digitized micrographs of the X₁-X₃ face of each section were acquired. The fiber angle, alpha (α), between the local muscle fiber axis (X₃; Figure 2) and the circumferential axis (X₁; Figure 2)
was measured at 5 sites on each image using image-processing software (SPOT Advanced Version 4.0.1; Diagnostic Instruments, Inc, Sterling Heights, Mich) such that mean \( \frac{\text{characterized the fiber angle at each transmural depth.}}{} \)

Two parallel cuts separated by \( \pm 1 \) mm were then made normal to the fiber axis in each of these transmural sections. The samples were kept moist with a 30% sucrose solution to avoid the distortional effects of dehydration and to minimize freezing artifact during direct histological measurements of sheet angle, beta (\( \beta \)), from the sheet-normal (S-N) plane. The fiber-normal slices were placed in 15-mm \( \times 15 \)-mm plastic molds (Tissue-Tek; Cryomold Intermediate, Miles Inc, Elkhart, Ind), embedded in OCT compound (Tissue-Tek; Sakura Finetek USA Inc, Torrance, Calif), frozen over dry ice, then stored for 2 to 4 days in an \( -80^\circ \) freezer. The myocardial slices were then cut into 8- to 10-\( \mu \)m-thick sections using a cryostat (Jung Frigocut 2800 N; Leica Inc, Germany) and transferred to a glass slide where they were imaged immediately with a digital camera (RT Color, 1X HRD 100-NIK; Diagnostic Instruments, Inc, Sterling Heights, Mich) mounted on a light microscope (Leica Type 301–371.010; Leica Inc, Germany) at \( 25 \times \) magnification. Myolaminae coursing in the direction noted from the frozen specimen were observed (defined as sheets) and, over a 1-minute period, gaps between the cleavage planes appear between the myolaminae. Using image-processing software, 5 \( \beta \) angles were measured between sheet orientations (\( X_\beta \)) and \( X_1 \) normal to the endocardial face, over the length of the specimen, and average \( \beta \) characterized the sheet angle at each transmural depth.

Hemodynamics and Cardiac Cycle Timing

Three consecutive steady-state beats in sinus rhythm were selected for analysis for control and annular suture pull (ASP) conditions from each study. Instantaneous LV volumes were calculated every 16.7 ms from the 3-D coordinates of the epicardial LV markers (Figure 1) by summing the volumes of multiple space-filling tetrahedra. For each cardiac cycle, ED was defined as the videofluoroscopic frame immediately before the upstroke of the LV pressure curve, defined as LV \( \frac{dP}{dt} \geq 120 \) mm Hg/s. ES was defined as the videofluoroscopic frame when LV \( \frac{d^2P}{dt^2} \) changed sign from minus to plus, a definition that captures the onset of isovolumic relaxation.

Cardiac Finite Strains

Cardiac normal and shear strains were calculated at 20%, 50%, and 80% depths from the epicardium, with ED as the reference configuration and ES as the deformed configuration. Detailed strain analysis methodology has been described previously.5

Sheet Finite Strains

As previously described,6 3 consecutive beats and at each transmural depth in each heart, cardiac finite strains (ie, relative to \( X_1, X_2, \) and \( X_3 \); Figure 1) at that depth were transformed into sheet strains at that depth oriented along the fiber (F), sheet (S), and sheet-normal (N) axes by application of the fiber (\( \alpha \)) and sheet (\( \beta \)) angle measurements in that heart at that depth as

\[
\begin{bmatrix}
E_{\text{ff}} & E_{\text{fs}} & E_{\text{fn}} \\
E_{\text{fs}} & E_{\text{ss}} & E_{\text{sn}} \\
E_{\text{fn}} & E_{\text{sn}} & E_{\text{nn}}
\end{bmatrix}
= \begin{bmatrix}
\cos \alpha & \sin \alpha & 0 \\
-\sin \alpha \sin \beta & \cos \alpha \sin \beta & \cos \beta \\
\sin \alpha & -\cos \alpha \cos \beta & \sin \beta
\end{bmatrix}
\begin{bmatrix}
E_{11} & E_{12} & E_{13} \\
E_{12} & E_{22} & E_{23} \\
E_{13} & E_{23} & E_{33}
\end{bmatrix}
\begin{bmatrix}
\cos \alpha & -\sin \alpha \sin \beta & \sin \alpha \cos \beta \\
\sin \alpha & \cos \alpha \sin \beta & -\cos \alpha \cos \beta \\
0 & \cos \beta & \sin \beta
\end{bmatrix}
\]

and the contribution of sheet strains to radial thickening \( E_{33} \) strain by

\[
E_{33} = E_{\text{ss}} \cos^2 \beta + E_{\text{nn}} \sin^2 \beta + 2E_{\text{sn}} \sin \beta \cos \beta
\]
**Mitral Annular Dimensions and Dynamics**

Septal-lateral annular diameter was calculated as the distance between the septal and mid-lateral annular marker in 3-D space (Figure 1). Commissure–commissure mitral annular diameter was calculated as the distance between the markers at the anterior commissure and posterior commissure in 3-D space.

**Statistical Analysis**

Data are reported as mean ± 1 SD. Sheet strains were compared using 2-way repeated measures ANOVA with Holm-Sidak pairwise multiple comparisons (Sigmastat 3.11; SPSS Inc, Chicago, Ill). ED and ES strains were compared with zero using a 1-sample t test. Group mean annular dimensions and dynamics were compared between baseline and ASP using 2-tailed t test for paired observation. *P<0.05 was considered statistically significant.

**Results**

Mean hemodynamic data before (control) and during cinching of the mitral suture annuloplasty (ASP) are listed in Table 1. Tightening the simulated annuloplasty decreased LV dP/dt max, EDV, and SV; ESV did not change significantly. Thus, LV preload decreased with ASP, which probably accounted for the decline in LV dP/dt max, which is preload-dependent. As expected, ASP altered the mitral valve geometry by reducing both the septal-lateral (≈20%) and the commissure–commissure (≈20%) mitral annular dimensions (Table 1).

Table 2 summarizes fiber-sheet systolic strains in the anterobasal LV wall (ED reference configuration; ES deformed configuration) at 20% (subepicardium), 50% (midwall), and 80% (subendocardium) wall depth. ASP reduced subendocardial systolic fiber shortening (E fs) (Table 2) and transmural systolic shear strain (E ss). Midwall sheet extension and subepicardial and subendocardial systolic shear thickening (E sn) were also lower after annuloplasty cinching. ASP had no effect on systolic fiber-sheet normal and shear strains in the lateral equatorial region, remote from the mitral annulus (Table 3).

Tables 4 and 5 show the fiber-sheet remodeling strains at ED and ES in the anterobasal and lateral equatorial regions, respectively. With ASP, anterobasal subendocardial fiber length was shorter at ED (Figure 3), consistent with the decrease in subendocardial systolic fiber shortening (E sn) (Figure 4a) by the Frank-Starling principle. In the lateral equatorial LV wall, remote from the mitral annulus, under-

TABLE 1. Hemodynamics and Mitral Annular Geometric Data During Control and ASP Conditions

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>ASP</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (min⁻¹)</td>
<td>116±18</td>
<td>122±27</td>
</tr>
<tr>
<td>EDP (mm Hg)</td>
<td>23±13</td>
<td>22±11</td>
</tr>
<tr>
<td>EDV (mL)</td>
<td>194±40</td>
<td>185±44*</td>
</tr>
<tr>
<td>dP/dt max (mm Hg/sec)</td>
<td>3084±810</td>
<td>2757±797*</td>
</tr>
<tr>
<td>LW max (mL)</td>
<td>195±40</td>
<td>187±43*</td>
</tr>
<tr>
<td>LVP max (mm Hg)</td>
<td>122±13</td>
<td>118±13</td>
</tr>
<tr>
<td>ESP (mm Hg)</td>
<td>103±12</td>
<td>98±14</td>
</tr>
<tr>
<td>ESV (mL)</td>
<td>141±32</td>
<td>143±32</td>
</tr>
<tr>
<td>LV min (mL)</td>
<td>138±31</td>
<td>140±32</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>54±13</td>
<td>42±17*</td>
</tr>
<tr>
<td>LVP min (mm Hg)</td>
<td>5±7</td>
<td>10±4</td>
</tr>
<tr>
<td>S-L diameter at ES (cm)</td>
<td>2.48±0.21</td>
<td>2.01±0.14*</td>
</tr>
<tr>
<td>C-C diameter at ES (cm)</td>
<td>3.60±0.46</td>
<td>2.95±0.42*</td>
</tr>
<tr>
<td>S-L max (cm)</td>
<td>2.64±0.34</td>
<td>2.10±0.16*</td>
</tr>
<tr>
<td>C-C max (cm)</td>
<td>3.88±0.43</td>
<td>3.09±0.42*</td>
</tr>
<tr>
<td>S-L min (cm)</td>
<td>2.39±0.19</td>
<td>1.96±0.14*</td>
</tr>
<tr>
<td>C-C min (cm)</td>
<td>3.56±0.43</td>
<td>2.90±0.43*</td>
</tr>
</tbody>
</table>

*P<0.05; **P<0.005.

C-C diameter at ES indicates commissure–commissure annular diameter at end-systole; C-C max, maximum commissure–commissure annular diameter; C-C min, minimum commissure–commissure annular diameter; ED, end-diastolic pressure; EDV, end-diastolic volume; +dP/dt max, maximum time derivative of left ventricular pressure (LVP); ESP, end-systolic pressure; ESV, end-systolic volume; HR, heart rate; LW, left ventricular volume; S-L diameter at ES, septal-lateral annular diameter at end-systole; S-L max, maximum septal-lateral annular diameter; S-L min, minimum septal-lateral annular diameter; SV=LV stroke volume.

**ED and ES Sheet Strains**

ED sheet strains were measured by comparing bead positions (in sheet coordinates) at ED from the control study (reference configuration, control) with the bead positions at ED during suture annuloplasty cinching (deformed configuration, ASP). ED sheet strains were calculated by comparing bead positions at ES in sheet coordinates from the control study (reference configuration) with the bead positions at ES during ASP (deformed configuration).

**TABLE 2. Transmural Systolic Fiber-Sheet Strains in the Anterobasal Region at 3 Different LV Wall Depths**

<table>
<thead>
<tr>
<th></th>
<th>Subepicardium</th>
<th>Midwall</th>
<th>Subendocardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=9</td>
<td>Control</td>
<td>ASP</td>
<td>Control</td>
</tr>
<tr>
<td>E fs</td>
<td>-0.08±0.07</td>
<td>-0.06±0.06</td>
<td>-0.11±0.09</td>
</tr>
<tr>
<td>E fn</td>
<td>0.00±0.04</td>
<td>0.00±0.04</td>
<td>0.22±0.12</td>
</tr>
<tr>
<td>E sn</td>
<td>0.16±0.15</td>
<td>0.09±0.08*</td>
<td>0.02±0.12</td>
</tr>
<tr>
<td>E es</td>
<td>0.03±0.05</td>
<td>0.01±0.03</td>
<td>-0.03±0.04</td>
</tr>
<tr>
<td>E ss</td>
<td>0.03±0.09</td>
<td>0.01±0.04</td>
<td>-0.03±0.04</td>
</tr>
<tr>
<td>E sn*</td>
<td>0.04±0.04</td>
<td>0.00±0.04</td>
<td>0.01±0.01</td>
</tr>
</tbody>
</table>

*P<0.05 ASP vs control at the same wall depth; RM ANOVA with Holm-Sidak pairwise multiple comparisons.

TABLE 3. Transmural Systolic Fiber-Sheet Strains in the Lateral Equatorial Region at 3 Different LV Wall Depths

<table>
<thead>
<tr>
<th></th>
<th>Subepicardium</th>
<th>Midwall</th>
<th>Subendocardium</th>
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</thead>
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<tr>
<td>n=9</td>
<td>Control</td>
<td>ASP</td>
<td>Control</td>
</tr>
<tr>
<td>E fs</td>
<td>0.12±0.09</td>
<td>0.06±0.04</td>
<td>0.11±0.04</td>
</tr>
<tr>
<td>E fn</td>
<td>0.00±0.04</td>
<td>0.00±0.04</td>
<td>0.11±0.04</td>
</tr>
<tr>
<td>E sn</td>
<td>0.16±0.15</td>
<td>0.09±0.08*</td>
<td>0.02±0.12</td>
</tr>
<tr>
<td>E es</td>
<td>0.03±0.05</td>
<td>0.01±0.03</td>
<td>0.00±0.05</td>
</tr>
<tr>
<td>E ss</td>
<td>0.03±0.09</td>
<td>0.01±0.04</td>
<td>0.00±0.05</td>
</tr>
<tr>
<td>E sn*</td>
<td>0.04±0.04</td>
<td>0.00±0.04</td>
<td>0.01±0.01</td>
</tr>
</tbody>
</table>

*P<0.05 ASP vs control at the same wall depth; RM ANOVA with Holm-Sidak pairwise multiple comparisons.
sized annuloplasty had no effect on fiber and sheet remodeling strains at ED and ES.

Table 6 and Figure 5 show the sheet components of systolic wall thickening in the anterobasal and lateral equatorial LV regions comparing control and ASP. Sheet shear (Esn) was found to be an important component of systolic wall thickening at all transmural depths at both sites studied. Unlike in the lateral equatorial region, undersized annuloplasty reduced sheet shear (Esn) in the anterobasal region at all three transmural depths by \( \approx 50\% \). Sheet thickening (Enn) also contributed significantly to systolic wall thickening in the LV subepicardium and subendocardium in the anterobasal region, whereas sheet extension was more important in the LV midwall layer. Undersized annuloplasty reduced sheet thickening in the anterobasal region by 61% in the subendocardium and sheet extension by 50% in the midwall. The fiber-sheet components of systolic wall thickening were not altered by undersized annuloplasty in the lateral equatorial region. Figure 6 illustrates the group means of fiber shortening (A), sheet thickening (B), sheet shear (C), and sheet extension (D) throughout the cardiac cycle in the subepicardium, midwall, and subendocardium within the anterobasal LV wall before and after tightening the adjustable annuloplasty.

### Discussion

Undersized mitral ring annuloplasty has been described as an “annular solution to a ventricular problem” in patients with functional or ischemic mitral regurgitation and congestive heart failure (CHF), caused by advanced dilated or ischemic cardiomyopathy.\(^1,2\) This procedure can reshape the ventricle into a more elliptical shape and may thereby reduce LV wall stress.\(^1,2\) A previous experiment from our laboratory showed that simulated mitral annuloplasty decreased LV circumferential radii of curvature at the basal, equatorial, and apical levels,\(^4\) but to make future progress a better understanding of transmural LV wall strains is necessary. Altered LV wall strains have been associated with production of cytokines and reactive oxygen species, which in turn stimulate myocyte apoptosis,\(^9–11\) disruption of extracellular matrix secondary to activation of matrix metalloproteinases,\(^12–14\) and extracellular fibrosis. These events are triggers that catalyze further global LV dilatation and adverse remodeling.\(^15–18\) Cheng et al from this laboratory\(^3\) demonstrated that the effects of undersized annuloplasty on myocardial cardiac strains differed by LV region. In the anterobasal LV wall close to the mitral annulus, wall thickness at ED increased and systolic radial strain (wall thickening, Es3) decreased at all transmural depths. Conversely, in the lateral equatorial LV region further from the annulus, LV transmural systolic and remodeling strains were virtually unchanged.\(^3\) Therefore, we now explored the effects of undersized annuloplasty in terms of myocardial fiber and sheet strains and mechanisms of LV wall thickening.

Streeter et al and others showed that fiber angle rotates across the LV wall, from a left-handed helix in the subepicardium to a right-handed helix in the subendocardium; in a helical wrapping pattern.\(^19\) These myocardial fibers are further grouped into laminar sheets, each being 3 to 4 cells thick,\(^20,21\) and laminar sheet dynamics contribute importantly to overall LV wall thickening. Costa et al found that systolic LV wall thickening results from 3 independent sheet mechanisms: sheet shear, sheet extension, and sheet thickening.\(^22\)

The principal finding of this study was that in the anterobasal LV wall, adjacent to the annulus, undersized annuloplasty reduced systolic wall thickening because of: (1) reduced end-diastolic fiber length and systolic fiber shortening in the subendocardium; and (2) decreased systolic sheet shear at all LV wall depths, sheet extension in the midwall, and sheet thickening in the subepicardium and subendocardium. Conversely, in the lateral equatorial level away from the annulus, undersized annuloplasty had no significant effect on LV wall thickening or on transmural fiber-sheet systolic or remodeling myocardial strains.

### Table 3. Transmural Systolic Sheet Strains in the Equatorial Lateral Region at 3 Difference Wall Depths

<table>
<thead>
<tr>
<th>Wall Depths</th>
<th>Subepicardium</th>
<th>Midwall</th>
<th>Subendocardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=9</td>
<td>Control ASP</td>
<td>Control ASP</td>
<td>Control ASP</td>
</tr>
<tr>
<td>Eₜ</td>
<td>-0.08±0.04</td>
<td>-0.07±0.06</td>
<td>-0.11±0.05</td>
</tr>
<tr>
<td>Eₚ₉</td>
<td>0.11±0.07</td>
<td>0.10±0.09</td>
<td>0.09±0.06</td>
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<tr>
<td>Eₚ₈</td>
<td>0.03±0.06</td>
<td>0.02±0.06</td>
<td>0.08±0.10</td>
</tr>
<tr>
<td>Eₚ₀</td>
<td>-0.01±0.07</td>
<td>0.00±0.05</td>
<td>0.02±0.03</td>
</tr>
<tr>
<td>Eₚₐ</td>
<td>0.01±0.02</td>
<td>0.00±0.01</td>
<td>-0.07±0.05</td>
</tr>
<tr>
<td>Eₚ₉₉</td>
<td>0.05±0.03</td>
<td>0.04±0.02</td>
<td>-0.12±0.06</td>
</tr>
</tbody>
</table>

Group mean (±SD) data from control and ASP from 9 hearts. No statistically significant differences between control and ASP.

![Figure 3. End-diastolic remodeling fiber length in anterobasal region from control to ASP conditions. Abscissa: wall depth. *P<0.05 from 2-tailed paired t test compared with zero.](image-url)
TABLE 4. Transmural LV Wall End-Diastolic Sheet Strains in the Anterobasal and Lateral Equatorial Regions

<table>
<thead>
<tr>
<th>Region</th>
<th>Control to ASP Conditions at ED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subepicardium</td>
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<tr>
<td>Anterobasal Region (n=9)</td>
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<tr>
<td>£sub</td>
<td>0.00±0.06</td>
</tr>
<tr>
<td>£ss</td>
<td>0.03±0.03</td>
</tr>
<tr>
<td>£sn</td>
<td>0.09±0.08</td>
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<tr>
<td>£sn</td>
<td>-0.01±0.02</td>
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<tr>
<td>£sn</td>
<td>-0.01±0.05</td>
</tr>
<tr>
<td>£sn</td>
<td>-0.03±0.05</td>
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<tr>
<td>Lateral Equatorial Region (n=9)</td>
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<tr>
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<tr>
<td>£ss</td>
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<tr>
<td>£sn</td>
<td>0.02±0.03</td>
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Group mean (±SD) data from 9 hearts for each region.

ED at reference configuration (control); ED at deformed configuration (ASP). P from 2-tailed paired t test comparing ASP values with zero.

Undersized mitral ring annuloplasty has been used in selected patient with FMR or IMR and CHF. Recent clinical studies in patients with FMR have shown that mitral regurgitation frequently recurs secondary to progressive LV remodeling,23–26 with suboptimal mid-term survival.27–29 Recurrent MR is often caused by continued LV remodeling and global dilatation, further papillary muscle displacement, and more apical leaflet tethering. Previous reports demonstrated that annuloplasty rings abolish normal mitral annular dynamics30 and restrict posterior mitral leaflet closing motion.31 Based on the present experiment, undersized annuloplasty does reduce MR and probably promotes LV reverse remodeling, but may compromise wall thickening mechanics adjacent to the mitral annulus.

After simulated undersized annuloplasty in this experimental preparation, myocardial ED fiber length was reduced in...
the subendocardium near the mitral valve in the anterobasal LV region. With less fiber preload, systolic fiber shortening is expected to decrease vis-à-vis the Frank-Starling principle; indeed, our data showed that subendocardial systolic fiber shortening was lower after annuloplasty in association with shorter end-diastolic fiber length. In addition to less systolic fiber shortening, laminar sheet mechanics were impaired. Our experimental data showed that laminar sheet shear is an important component of systolic wall thickening at all transmural depths. With sheet angle change, the myocardial sheets slide along each other and shear within the sheets contributes to systolic LV wall thickening.6 Annuloplasty reduced systolic sheet shearing in all LV wall layers, which significantly reduced systolic wall thickening. Sheet extension (fibers thickening and spreading apart from each other within the sheets) and sheet thickening also contribute to systolic wall thickening;6 in this ovine study, sheet extension (Eee) contributed significantly in the midwall, whereas sheet thickening (Enn) was more important in the subepicardial and subendocardial layers. Annuloplasty decreased sheet extension in the midwall and sheet thickening in both the subepicardium and subendocardium. These findings indicate that overcorrecting mitral annular dimensions may have an adverse effect on local LV systolic function in the anterobasal region close to the annulus. Both the mitral septal-lateral and commissure–commissure dimensions were reduced by 20% in this experiment. Dilatation of the mitral septal-lateral annular dimension is one of the key mechanisms producing IMR;32,33 we have previously shown that a simple septal-lateral transannular suture (“SLAC”) can reduce septal-lateral annulus size and eliminate acute IMR, while not perturbing normal mitral annular contraction, 3-D geometric annular dynamics, aortic-mitral annular flexion, or anterior leaflet excursion.33 A finite element study by Maisano et al34 suggested that selectively reducing the septal-lateral annular dimension is more effective in eliminating apical systolic leaflet tethering than is a conventional complete annuloplasty ring. It may be possible that newly designed disease-specific annuloplasty rings (eg, Edwards IMR ETlogix, Edwards Alfieri-Bolling Geoform, St. Jude Medical Rigid Saddle Ring [RSR]), which disproportionately and selectively reduce the mitral septal-lateral annular dimension (by 17% to 40%) may reduce anterobasal LV systolic wall thickening even more, but this is speculation and has not been studied experimentally or clinically.

In the lateral equatorial LV wall farther away from the annulus, LV transmural systolic wall thickening, systolic...
cardiac strains, systolic fiber-sheet strains, and remodeling fiber-sheet strains were all virtually unchanged. These data suggest that simulated annuloplasty, by itself, does not acutely influence myocardial strains in distant LV regions. Under-sized ring annuloplasty corrects Carpentier type I leaflet motion (annular dilation) and to some degree Carpentier type II (systolic leaflet apical tethering) leaflet motion which both are important components of IMR; however, a direct ventricular approach to reduce LV wall strains is probably also necessary to promote reverse LV remodeling. By attenuating shear strain abnormalities, stimulation of cytokines and reactive oxygen species, apoptosis, activation of matrix metalloproteinases, may be minimized. Even though many surgical treatments (Acorn CorCapTM© CSD, SAVR, and/or “Paco-pexy,” Fontan stitch, CoapsysTM, Menicanti tri-level reconstruction, papillary muscle sling, catheter interventional coronary sinus cerclage) aimed at reducing LV wall stress and strain and normalizing LV shape have been tried, a more comprehensive understanding of transmural LV fiber and sheet strain mechanics with respect to LV wall thickening will be important in the future to enhance the likelihood that surgical LV reconstructive procedures actually reverse the deleterious LV remodeling pathological and neurohumoral cascade. Finally, it should be emphasized that our acute, experimental findings do not imply that undersized ring annuloplasty be abandoned in patients with CHF caused by cardiomyopathy and FMR or IMR.

Limitations
Considerable caution must be exercised in extrapolating the results of this acute, open-chest experiment in normal sheep hearts to the clinical situation in which patients present with long-standing CHF, chronic IMR or FMR, and marked LV dilatation. Myocardial ischemia or infarction was not induced in this study, thus we did not examine the effects of myocardial injury on transmural LV fiber and sheet deformation and its response to simulated annuloplasty. In a previous study with a chronic closed chest model, Cheng et al17 has shown that posterior wall infarction not only increased longitudinal-radial shear and circumferential-radial shear strain in the myocardium adjacent to the infarct, but also increased longitudinal-radial shear strain in region remote from the infarct. From the result of this study, because undersized annuloplasty did not alter systolic cardiac strains, systolic fiber-sheet strains, and remodeling fiber-sheet strains further from the annulus at the equatorial level, we conjecture that under-sized annuloplasty alone would not be sufficient to correct the increased shear strains as seen in the chronic model. A combined ventricular surgical approach plus ring annuloplasty might therefore be necessary to repair annular dilatation, leaflet tethering, and altered shear strains, as observed in chronic IMR or FMR. Further investigation is needed. In addition, as described, although currently there are multiple newly designed disease-specific rigid, semi-rigid, and flexible annuloplasty rings (eg, Edwards IMR ETlogix, Edwards Alfieri-Bolling Geoform, St. Jude Medical Rigid Saddle Ring [RSR]), in this study we only examined the effect of simulated, reversible, undersized mitral annuloplasty on transmural LV wall deformations to allow comparison of baseline and annuloplasty data in the same animals.

Future studies are necessary to look at different annuloplasty rings, especially the rigid rings, to examine whether a “firm” fixation of the annulus can inhibit systolic basal wall thickening to an even greater degree or whether it can correct strain alterations in LV myocardium further away from the annulus.

As described in our previous article,⁶ although fiber angle (α) measurements are straightforward, sheet angle (β) measurement are often difficult. Multiple populations of β can be present at similar wall depths, particularly in the subendocardium. We used the dominant β for this analysis in this study.
Fiber-sheet dynamics differ regionally because of substantial regional variations in fiber and sheet distributions and geometries, our data represent fiber-sheet mechanics only in the anterobasal and lateral equatorial LV regions. Future work will be required to further characterize the functional importance of the multiple β populations and regional fiber and sheets geometrical differences throughout the entire left ventricular myocardium.

Figure 6. LV pressure (LVP) and anterobasal LV fiber shorting (A; $E_f$), sheet thickening (B; $E_{nn}$), sheet shear (C; $E_{ss}$), and sheet extension (D; $E_{ss}$) at subepicardium, midwall and subendocardium vs time from one heart in this study before (control) and after (ASP) tightening the adjustable annuloplasty.
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Disclosures
None.

References
Effects of Undersized Mitral Annuloplasty on Regional Transmural Left Ventricular Wall Strains and Wall Thickening Mechanisms
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