Mitral Annular Dilatation and Papillary Muscle Dislocation Without Mitral Regurgitation in Sheep

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Background—Asymmetrical mitral annular (MA) dilatation and papillary muscle dislocation are implicated in the pathogenesis of functional mitral regurgitation (MR).

Methods and Results—To determine the mechanism by which annular and papillary muscle geometric alterations result in MR, we implanted radiopaque markers in the left ventricle, mitral annulus, anterior and posterior mitral leaflets, and papillary muscle tips and bases in 2 groups of sheep. One group served as controls (CTL, n = 7); an experimental group (EXP, n = 9) underwent topical phenol application to obliterate anterior annular and leaflet muscle (confirmed histologically ex vivo). After 1 week of recovery, markers were imaged with biplane videofluoroscopy, and hemodynamic data were recorded. MA area (computed from 3-dimensional marker coordinates) was 11% to 13% larger in the EXP group than in the CTL group (P < 0.05 by ANOVA). This area increase resulted exclusively from intercommissural axis increase except in 1 heart with large (>1 cm) increases in both the intercommissural and septolateral annular axes. The anterior papillary muscle tip in EXP was displaced from CTL by 2.9 ± 0.23 mm toward the anterolateral left ventricle and 2.5 ± 0.12 mm toward the mitral annulus at end systole; the posterior papillary muscle geometry was unchanged. Transthoracic echocardiography revealed MR only in the heart exhibiting biaxial annular enlargement.

Conclusions—MA dilatation in the intercommissural dimension with anterior papillary muscle tip displacement toward the annulus is insufficient to produce MR in sheep. Functional MR may require MA dilatation in the septolateral axis, as observed with proximal circumflex coronary occlusion. (Circulation. 1999;100[suppl II]:II-95–II-102.)

Key Words: mitral valve • regurgitation • surgery

The mitral valve requires precise coordinated function of the left atrium, mitral annulus, leaflets, papillary muscles, and left ventricle (LV) to close without leakage. Mitral regurgitation (MR) often results from dysfunction of 1 or more of these components. The relative importance of individual subunit dysfunction in the pathogenesis of MR remains poorly understood, and changes in the mitral annulus that may contribute to MR are particularly ambiguous. Although mitral annular (MA) dilatation often accompanies MR, the proposed mechanism by which this finding produces MR varies according to the cause of MR. In ischemic MR, MA dilatation is frequently associated with alterations in the subvalvular apparatus and regional or global LV dysfunction. There is speculation as to which distortions of the mitral valve that were created. An experiment was performed in sheep to test the hypothesis that mild to moderate annular dilatation was sufficient to compromise mitral valve competence and result in MR.

Methods

Two groups of adult castrated male sheep were used in this experiment. Data from a control group (CTL, n = 7, 67 ± 8 kg, mean ± 1 SD) were compared with an experimental group (EXP,
The left carotid artery and right atrium were cannulated, and the heart was suspended in a saline bath containing crystalloid cardioplegia. Through a left atriotomy, 8 tantalum radiopaque markers were inserted into the epicardium and septum as previously described. Epicardial echocardiography with color Doppler flow analysis was also used to assess initial competence and anatomy of the mitral valve. Figure 1A illustrates the myocardial marker array analyzed in this experiment. (See text for anatomic description of marker locations.)

Figure 1. A, Array of radiopaque markers used in experiment. APM indicates anterior papillary muscle; and PPM, posterior papillary muscle. B, Expanded view of annular and leaflet marker placement. RFT indicates right fibrous trigone; LFT, left fibrous trigone; AML, anterior mitral leaflet; and PML, posterior mitral leaflet. (See text for anatomic description of marker locations.)

Surgical Preparation

Sixteen sheep were premedicated with ketamine (27 mg/kg IM) and atropine sulfate (0.05 mg/kg IV) for the placement of percutaneous IV and arterial lines. A micromanometer-tipped pressure transducer (SPC-500; Millar Instruments, Inc) was zeroed and used to monitor systemic arterial blood pressure as anesthesia was induced with sodium thiopental (6.8 mg/kg IV). The animals were then intubated, placed on mechanical ventilation (Servo Anesthesia Ventilator; Siemens-Elema AB) with supplemental oxygen; general anesthesia was maintained with inhalational isoflurane (1% to 2.2%). A left thoracotomy was performed through the fifth intercostal space, and pneumatic occluders (In Vivo Metric Systems) were placed around the superior and inferior vena cavae. The heart was suspended in a pericardial cradle, and 2 miniature radiopaque tantalum markers (ID 0.8 mm, OD 1.3 mm, length 1.5 to 3.0 mm) were inserted into the LV epicardium and septum as previously described. Epicardial echocardiography with color Doppler flow analysis was also used to assess initial competence and anatomy of the mitral valve. Figure 1A and 1B illustrates the myocardial marker array analyzed in this experiment.

The animals were anticoagulated with heparin sulfate (300 IU/kg). The left carotid artery and right atrium were cannulated, and the animal was placed on cardiopulmonary bypass. The aorta was cross-clamped, and the heart was arrested with cold antegrade crystalloid cardioplegia. Through a left atriotomy, 8 tantalum radiopaque markers were sutured 45 degrees from each other around the circumference of the mitral annulus. Four markers were sutured along the central meridian of the anterior mitral leaflet from the annulus to the leaflet edge; similarly, 2 markers were sutured to the central meridian of the middle cusp of the posterior leaflet from the annulus to the leaflet edge. Two markers were placed at the tips of the anterior and posterior papillary muscles. A solution of 95% phenol (P-1037; Sigma Chemical Co), a histotoxic chemical, was applied to a small band of muscle located along the anterior mitral annulus in sheep in the EXP group for 2 minutes until the treated area turned pale. This muscle is thought to be an important modulator of MA area (MAA) and geometry. An implantable micromanometer-pressure transducer (PA4.5-X6; Konigsberg Instruments, Inc) was then placed in the LV chamber through the apex. The aortic cross-clamp was released, and the heart was deaired. The atriotomy and cardioplegia sites were next closed, and the animal was weaned from cardiopulmonary bypass and decannulated. Chest tubes were placed, and the thoracotomy was closed. The animal was placed in the experimental animal cardiac surgical intensive care unit to recover and receive hydromorphone hydrochloride (Dilaudid 0.03 mg/kg IV; Knoll Pharmaceuticals) for postoperative analgesia.

Experimental Design

After a recovery period (8±1 day, mean±1 SD), each animal was taken to the experimental animal cardiac catheterization laboratory for study. The animals were premedicated with ketamine, intubated, and mechanically ventilated (ventricular anesthesia ventilator 2000; Hallowell EMC) with 100% oxygen. Ketamine (1 to 4 mg · kg⁻¹ · h⁻¹ IV infusion) and diazepam (5-mg IV bolus as needed) were administered as necessary to maintain the animal in a sedated state. A micromanometer-tipped catheter (Millar MPC-500; Millar Instruments) previously zeroed in a 37°C water bath was placed in the descending thoracic aorta to measure aortic pressure. Heart rate was slowed by the administration of UL-FS49 (a highly specific negative chronotropic agent that does not alter the inotropic state or blood pressure; Boehringer-Ingelheim), esmolol (20 to 40 μg · kg⁻¹ · min⁻¹ IV infusion), and atropine (to abolish sympathetic response) to a target rate between 90 and 110 bpm to facilitate videofluoroscopic visualization and tracking of the miniature radiopaque myocardial markers. Transthoracic echocardiography with color Doppler and contrast left ventriculography were performed to determine the competence of the mitral valve.

Simultaneous biplane videofluoroscopic and hemodynamic data were acquired with the animal in the right lateral decubitus position under steady-state conditions. All animals were studied in normal sinus rhythm with ventilation briefly arrested at end expiration to minimize the effects of respiratory variation. Data were collected in the baseline autonomically blocked state under normal loading conditions and during caval occlusion to alter preload.

All animals received humane care in compliance with the “Principals 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 (DHEW NIH publication No. 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.

Data Acquisition and Reduction

A Philips Optimus 2000 biplane Lateral ARC 2/poly DIAGNOST C2 system (Philips Medical Systems, North America Company) was used to collect videofluoroscopic data at 60 Hz with the image intensifiers in the 9-inch mode. Two-dimensional images from each of the 2 radiographic views (45-degree right anterior oblique and 45-degree left anterior oblique) were digitized and merged to yield 3-dimensional coordinates for each radiopaque marker every 16.7 ms with the use of custom-designed software. The details of this data reduction procedure have been published previously. The descending thoracic aortic pressure, LV pressure, and ECG voltage were simultaneously digitized and recorded in real-time on the video images during data acquisition.

Data Analysis

Two consecutive baseline beats were analyzed from each of the 16 hearts. Three time points in each cardiac cycle were then analyzed:
For mitral leaflet markers, the \( y \) axis is defined from the LV apex through the midpoint of a line between markers 18 and 22 (\( x \) axis), with the \( z \) axis (not shown) orthogonal to the \( x \) and \( y \) axes. For papillary tip markers, \( r \) is distance from \( y \) axis (positive is away from \( y \) axis), and \( \phi \) is angular rotation of \( r \) around \( y \).

(1) T1 (mid-systolic contraction), defined as the videofluoroscopic frame preceding \( \frac{dP}{dt_{\text{max}}} \); (2) T2 (mid-LV ejection), defined as the frame preceding 50% LV stroke volume; and 3) T3 (early isovolumic relaxation), defined as the frame preceding \( \frac{dP}{dt_{\text{min}}} \). Data are reported as mean ± SD unless otherwise stated.

At each of the 3 time points, marker centroid coordinates were rotated and translated from their original laboratory reference frame to a cylindrical coordinate system (Figure 2).

**Hemodynamic Indices**

The time derivative of the LV pressure signal was used to determine peak positive \( \frac{dP}{dt} \) (\( \frac{dP}{dt_{\text{max}}} \)) and peak negative \( \frac{dP}{dt} \) (\( -\frac{dP}{dt_{\text{max}}} \)). For each cardiac cycle, end diastole was defined as the videofluoroscopic frame containing the peak of the ECG R wave, and end systole was defined as the frame preceding \( -\frac{dP}{dt_{\text{max}}} \). Data are reported as mean ± SD unless otherwise stated.

LV Volume

Instantaneous LV volume was estimated every 16.7 ms from the epicardial LV markers according to a space-filling multiple tetrahedral volume method. The details of this method have been previously published.19

LV Systolic Performance

Global LV systolic function was assessed through calculation of preload-recruitable stroke work (PRSW). External LV SW was calculated as the integral of LV pressure (\( P \)) multiplied by volume over a cardiac cycle for several beats at baseline and during caval occlusion as

\[
\text{SW} = \int P \, dV
\]

PRSW was then obtained through linear regression of SW on end-diastolic volume as

\[
\text{SW} = M_x (EDV - V_u)
\]

where \( M_x \) and \( V_u \) are the slope and volume axis intercept, respectively.

**MAA and MA Axes**

The distance between adjacent annular markers was computed from individual 3-dimensional marker coordinates at each of the 3 time points. MAA was calculated as the product of 8 triangular areas, each defined with 2 adjacent annular markers, and the center of mass of all 8 annular markers (centroid of the mitral annulus). No assumptions regarding annular geometry were required with this method. The length of the septolateral (SL) and the commissure/commissure (CC) axes were computed from 3-dimensional MA marker coordinates (Figure 3).

**Papillary Muscle Tip Geometry**

The cylindrical coordinates \( (r, y, \phi) \) of the anterior and posterior papillary muscle tip markers were computed as described in Data Analysis. These coordinates were then compared between the groups at T1, T2, and T3.

**Mitral Leaflet Position and Shape**

At each of the 3 sample times, the angle was calculated between an annular reference vector (defined from marker 22 to marker 18) and the vector from annular marker 22 to anterior leaflet marker 34 (\( \theta_{34} \); Figure 4A). The angle between the same annular reference vector and a vector to posterior leaflet marker 35 was also computed (\( \theta_{35} \); Figure 4A). An estimate of the shape of the anterior and posterior mitral leaflets at each of the 3 time points was assessed by plotting the projection of the centroid of all leaflet markers in the \( x-y \) plane (Figure 4B).

**Statistical Analysis**

For each variable, data from all 3 time points (T1, T2, and T3) for each group were compared with the use of ANOVA. Variables with values of \( P<0.05 \) by ANOVA were then compared between the 2 groups with the use of a 2-tailed Student’s \( t \) test. Differences within each group at different time points were tested with the use of repeated measures ANOVA. The level of significance for statistical comparison was set at \( P<0.05 \).

**Results**

Animal weight (CTL 67±8, EXP 69±8; \( P=\text{NS} \)) was not different between the 2 groups. Postmortem examination
revealed that all 8 MA markers were within 1 mm of the mitral annulus, defined as the mitral leaflet/left atrial junction, in both groups.

### Hemodynamics

Mean hemodynamic data for all animals in each group at each of the 3 time points are summarized in Table 1. Heart rate was 13% higher in the EXP group \((P=0.05)\) and LV end-systolic pressure was significantly lower in the EXP group compared with the CTL group; more specifically, LVP was lower at T2 \((P=0.002)\) and T3 \((P=0.004)\). LV volume at end diastole and end systole, stroke volume, ejection fraction, and dP/dt max were not significantly different between the 2 groups at any time. The slope of the PRSW relation, Mw, was significantly lower \((P=0.02)\) in the EXP group by 26%.

### Mitral Annulus

Figure 5 illustrates LVP and MAA for 2 cardiac cycles in 1 representative animal from each of the CTL and EXP groups. Note that MAA in the EXP animal was much higher than that of the CTL animal at all times. Values for MAA in CTL and EXP animals at each of the 3 time points are shown in Table 2. The MAA in the EXP group was 15% larger at T1 \((P=0.046)\), 16% larger at T2 \((P=0.03)\), and 17% larger at T3 \((P=0.02)\) compared with the CTL group. The increased MAA resulted exclusively from an increase in the CC dimension in the EXP group (Table 2). There were no significant differences between the groups in the SL dimension at each of the 3 time points, whereas the CC dimension increased 10% at T1 \((P=0.001)\), 10% at T2 \((P=0.008)\), and 11% at T3 \((P=0.01)\) from CTL to EXP.

Histological changes in the area of the anterior mitral annulus treated with phenol were evaluated with trichrome staining of specimen taken from that region at necropsy in each animal. Figure 6 shows the location of the mitral valve muscle that was treated with phenol. Contraction bands, pyknotic nuclei, and hypereosinophilia were noted in the superficial 50% to 75% of the treated muscle in EXP animals (Figure 7).

### Papillary Muscles

The coordinates of the anterior and posterior papillary muscle tips at each of the 3 time points from CTL and EXP are summarized in Table 3. There was no difference in the 3-dimensional position of the posterior papillary muscle between the 2 groups at any time. The anterior papillary muscle tip, however, was located farther away from the reference axis, toward the anterolateral LV \((\Delta y=3.1\, \text{mm})\) \((T1\, P=0.03,\, T2\, P=0.03,\, T3\, P=0.04)\) and closer to the annulus \((\Delta y=2.7\, \text{mm})\) \((T1\, P=0.01,\, T2\, P=0.01,\, T3\, P=0.01)\) at each of the 3 time points.

### Left Ventricle

LV volume was not significantly different at each of the 3 time points \((\text{CTL}:\, T1\, 178\pm51,\, T2\, 164\pm47,\, T3\, 150\pm43\, \text{mL};\, \text{EXP}:\, T1\, 203\pm37,\, T2\, 188\pm36,\, T3\, 171\pm35\, \text{mL};\, P=\text{NS})\). The fact that LV volume was not different at each of the 3 time points in both groups strongly suggests that LV size was not

### Table 1. Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>CTL</th>
<th>EXP</th>
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<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>99±11</td>
<td>114±14*</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>13±7.4</td>
<td>16±7.7</td>
</tr>
<tr>
<td>LVESEPV, mm Hg</td>
<td>93.2±13.2</td>
<td>76.5±12.2*</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>180±51</td>
<td>206±38</td>
</tr>
<tr>
<td>LVESEV, mL</td>
<td>149±43</td>
<td>170±35</td>
</tr>
<tr>
<td>SV, mL</td>
<td>31±9</td>
<td>36±11</td>
</tr>
<tr>
<td>EF</td>
<td>0.17±0.03</td>
<td>0.18±0.05</td>
</tr>
<tr>
<td>dP/dtmax, mm Hg/s</td>
<td>1621±402</td>
<td>1266±291</td>
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<tr>
<td>Mw, mm Hg</td>
<td>72.1±14.3</td>
<td>52.7±14.6*</td>
</tr>
<tr>
<td>Vm, mL</td>
<td>133±41</td>
<td>149±36</td>
</tr>
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</table>

LVEDP indicates LV end-diastolic pressure; LVESEPV, LV end-systolic pressure; LVEDV, LV end-diastolic volume; LVESEV, LV end-systolic volume; SV, stroke volume; and EF, ejection fraction.

Values given as mean±1 SD.

*P<0.05 by Student’s t test.

### Table 2. Mitral Annular Area and Axes

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T2</td>
</tr>
<tr>
<td>MAA, cm²</td>
<td>7.1±0.6</td>
<td>7.0±0.5</td>
</tr>
<tr>
<td>MA SL, cm</td>
<td>2.6±0.1</td>
<td>2.6±0.1</td>
</tr>
<tr>
<td>MA CC, cm</td>
<td>3.5±0.2</td>
<td>3.5±0.2</td>
</tr>
</tbody>
</table>

Values are mean±1 SD.

*P<0.05 by Student’s t test.
different and that myocardial markers were consistently placed in close anatomic proximity between different hearts.

**Mitral Leaflets**
The angular relation of the anterior and posterior mitral leaflet edges with respect to the annulus ($\theta_{a}$ and $\theta_{p}$) was not significantly different between the groups at any of the 3 time points (Table 4). The shape of the closed anterior and posterior mitral leaflets also was not significantly different at the 3 time points within each group, and there was no difference in either anterior or posterior leaflet shape from T1 to T3 within each group (Figure 8).

**Mitral Valve Competence**
All 16 animals each underwent epicardial echocardiography with color Doppler at the time of the initial operation and a transthoracic study as well as contrast left ventriculography at

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**TABLE 3. Three-Dimensional Anterior and Posterior Papillary Muscle Tip Position**

<table>
<thead>
<tr>
<th></th>
<th>CTL</th>
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<th>EXP</th>
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<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T2</td>
<td>T3</td>
<td>T1</td>
<td>T2</td>
<td>T3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Anterior</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r, cm</td>
<td>1.89±0.22</td>
<td>1.87±0.23</td>
<td>1.81±0.23</td>
<td>2.22±0.24*</td>
<td>2.18±0.23*</td>
<td>2.11±0.24*</td>
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</tr>
<tr>
<td>y, cm</td>
<td>2.41±0.13</td>
<td>2.41±0.12</td>
<td>2.41±0.13</td>
<td>2.12±0.18*</td>
<td>2.15±0.18*</td>
<td>2.15±0.19*</td>
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<tr>
<td>$\phi$, degrees</td>
<td>94.0±13.8</td>
<td>95.7±13.2</td>
<td>95.7±12.6</td>
<td>107.1±13.2</td>
<td>107.1±13.2</td>
<td>107.1±12.6</td>
<td></td>
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<tr>
<td>Posterior</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r, cm</td>
<td>0.73±0.29</td>
<td>0.54±0.23</td>
<td>0.46±0.14</td>
<td>0.86±0.26</td>
<td>0.61±0.24</td>
<td>0.47±0.23</td>
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<tr>
<td>y, cm</td>
<td>3.14±0.23</td>
<td>3.21±0.24</td>
<td>3.22±0.24</td>
<td>3.18±0.29</td>
<td>3.19±0.28</td>
<td>3.22±0.28</td>
<td></td>
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<tr>
<td>$\phi$, degrees</td>
<td>229.8±24.6</td>
<td>213.1±48.1</td>
<td>196.0±70.5</td>
<td>263.6±23.5</td>
<td>264.1±32.7</td>
<td>229.8±90.0</td>
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</tbody>
</table>

Values are mean±1 SD.
*P<0.05 by Student’s t test.

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**Figure 6.** Low-power (×4) photomicrograph showing location of mitral valve muscle in 1 sheep (arrow). LA indicates left atrium; MA, mitral annulus; and AL, anterior leaflet.

**Figure 7.** Photomicrograph of specimen (trichrome stain) taken from phenol-treated mitral anterior leaflet muscle in EXP group. Note subannular band of myocytes showing acute injury with hyper eosinophilic cytoplasm and small pyknotic nuclei (arrow). Normal myocytes are shown adjacent to damaged myocytes. (×).
the time of data acquisition to assess mitral valve competence. Three of the animals in the CTL group and 4 animals in the EXP group had trace MR on the basis of epicardial echocardiography at the time of surgery that was not present at the time of data acquisition, 1 week after surgery. Only 1 animal in the EXP group developed significant MR, which was graded as 2+. The findings in this animal are interesting with respect to variables reported from the EXP group mean (see Discussion).

### Discussion

Alterations in the mitral valve that lead to MR appear heterogeneous and depend on the cause and pathophysiology of disease. Postulated mechanisms for MR include (1) alteration in MA size or shape, (2) disorientation or discoordination of the papillary muscles relative to the annulus, and (3) LV dysfunction, dilatation, or both.9,20 –22 The relative importance of altered function of each mitral complex subunit to the creation of MR remains obscure, and experimental evaluation of individual component dysfunction is lacking. In this experiment, we sought to alter the mitral annulus to determine whether such changes could produce MR. The average 16% increase in MAA observed in the EXP group at all 3 time points was created by treating a little known heterogeneous muscle band that runs along the anterior mitral annulus with phenol. Originally described by Cooper et al23 in dogs, this muscle in some detail. Recently, Marron et al24 performed pathology studies in humans and described this muscle in some detail.

Although MAA was significantly larger in the EXP group in this experiment, MR was observed in only 1 EXP animal, which was an extreme outlier. It seems that the MA dilatation was insufficient to produce MR in this experiment, but annular enlargement occurred exclusively in the CC dimension without significant alteration of the SL dimension. Could it be that only increases in MAA due to asymmetrical annular dilatation or increase in the SL dimension lead to MR? Previous studies of acute ischemic MR yield provocative insight into the relative importance of annular dilatation and shape change that produce MR. In an ovine model of acute ischemic MR, Gorman et al21 created 2 to 3+ MR through infarction of 32% of the posterior LV. Sonomicrometer array localization revealed that postinfarction MR was the result of several small changes in mitral valve complex subunits as follows: (1) asymmetrical posterior annular enlargement, (2) decreased posterior papillary muscle contraction with displacement of the posterior papillary muscle tip 1.5±0.3 mm closer to the posterior commissure and 1.9±0.3 mm closer to the annulus, and (3) asymmetrical LV dilatation. Specifically, MA circumference was noted to increase 4.6% and 5.3% at end diastole and end systole after infarction, respectively, and the change in circumference occurred mainly in the posterior regions. Whether this circumference change resulted in an increased SL or CC dimension was not reported.22 In a later experiment from that same group with the same ovine model, MAA was found to increase 9.2±6.3% at end systole after posterior LV infarction and the creation of 2 to 3+ MR. In this experiment, the distance between the anterior and posterior commissures increased by only 1.4% (P=NS), and the distance between a diameter orthogonal to the line of leaflet coaptation increased an average of 2.3 mm (P<0.05).21 Similar results were obtained in our laboratory with both ovine and canine models of acute ischemic MR. MAA increased from 4.9±0.8 to 5.9±0.6 cm² (P<0.05) after posterolateral ischemia, with nearly all of the area increase resulting from an increased SL dimension without a significant change in the CC dimension.5 There appears to be a positive correlation between MA enlargement due to an increase in the SL dimension and MR. Changes observed in the subvalvular apparatus in these experiments, however, weaken this correlation.

In the work by Gorman et al,21 the anterior papillary muscle tip was observed to move away from the MA plane at end systole after infarction by 0.9±0.7 mm, and the posterior

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**TABLE 4. Anterior and Posterior Mitral Leaflet Edge Position Relative to an Annular Reference Vector at 3 Systolic Time Points (θMa, θMc; see Figure 4B)**

<table>
<thead>
<tr>
<th></th>
<th>CTL</th>
<th></th>
<th>EXP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T2</td>
<td>T3</td>
</tr>
<tr>
<td>θMa, degrees</td>
<td>40.4±8.2</td>
<td>33.6±4.4</td>
<td>33.8±6.3</td>
</tr>
<tr>
<td>θMc, degrees</td>
<td>67.9±8.6</td>
<td>58.8±9.8</td>
<td>57.0±10.6</td>
</tr>
</tbody>
</table>

Values are mean±1 SD. *P<0.05 by Student’s t test.

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**Figure 8.** Two-dimensional plot of anterior and posterior leaflet marker centroids and annular reference markers (18 and 22). Centroids of markers represent mean±SEM for all 3 time points; position of each marker was not different within groups at T1, T2, or T3.
papillary muscle moved closer to the centroid of the annulus at end systole. Given these changes in the subvalvular apparatus and because the calculated ratio of mitral leaflet area to MAA was 1.52±0.31, discoordination of papillary muscle contraction and position were thought to be primarily responsible for the MR created.28 Alterations in the subvalvular apparatus were also observed between the groups in our experiment. The anterior papillary muscle moved toward the anterior LV free wall and nearer the annular plane. It cannot be discerned whether this change was compensatory and prevented MR due to annular dilatation, but by the same logic used by Gorman et al,21,25 movement in the observed direction would tend to produce leaflet prolapse and, potentially, MR. Taken together, our results and those from the Penn group suggest that it is not simply mild to moderate annular dilatation that is a risk factor for MR but rather the specific annular geometric changes associated with annular dilatation. Even greater annular dilatation in our experiment failed to produce MR, but the dilatation was in a direction perpendicular to that observed by Gorman et al25 that resulted in MR. Alternatively, annular dilatation may simply be a contributing factor to the creation of MR, with alterations in the subvalvular apparatus being paramount, at least in these ovine models. Even changes in the subvalvular apparatus of similar magnitude to those observed by Gorman et al,25 but again on the opposite side of the heart (anterior versus posterior papillary muscle), failed to produce MR. Although certain disease processes like ischemia result in MR with 1- to 2-mm changes in certain components of the mitral valve complex, the system appears sufficiently robust to withstand larger changes when occurring in less critical subunits of the complex. The anterior LV and anterior papillary muscle seem to be more resilient areas of the mitral complex in that large acute anterior infarctions and smaller chronic infarctions in sheep both fail to produce MR and clinically anterior LV infarction is infrequently associated with MR.26

Because the degree and type of annular dilatation produced in our experiment did not result in MR, we speculate that mitral annuloplasty may relieve MR, at least in certain cases, by a mechanism other than decreased MAA and increased ratio of leaflet area to annular orifice area. Carpentier et al27 have maintained for years that MAA reduction is only 1 aspect of mitral valve repair and that the fix of the geometry of the mitral annulus in an end-systolic configuration may be equally important. In addition to MA shape, newer data show that the 3-dimensional relation of the mitral annulus to the subvalvular apparatus appears to be critical in the prevention of MR. In 31 patients undergoing mitral annuloplasty for functional ischemic MR, Liel-Cohen et al28,29 used 2-dimensional echocardiography and showed that despite equivalent MAA reduction, MR persisted in 18 patients and resolved in 13. There was a larger end-systolic volume and greater tethering distance from the papillary muscles to the anterior annulus in patients with MR. Mitral annuloplasty was thought to be effective in the 13 successful operations because the mitral annulus was brought into a more favorable geometry with respect to the subvalvular apparatus.28 In a chronic sheep model of ischemic MR, that same group used 3-dimensional echocardiography to assess valve competence, while the posterior papillary muscle was manually manipulated until MR was no longer apparent. Surgical plication of the infarcted area of myocardium was then performed to reorient the posterior papillary muscle to a position in which no MR occurred as determined with echocardiography.29 These are exciting observations in that surgical practice focuses on a reduction in annular area through the performance of mitral annuloplasty when in fact MA shape and the relation of the annulus to the subvalvular apparatus may be more important factors to consider.

The pathophysiology of MR that occurs in the setting of dilated cardiomyopathy is controversial. Bach and Bolling30 and Bolling et al31 recently published the results of mitral annuloplasty in 56 patients with MR and dilated cardiomyopathy. Annuloplasty alone, without alteration in the subvalvular apparatus, abolished MR in those patients. This seems to suggest that either annular dilatation alone was primarily responsible for MR or annuloplasty was effective for another reason. Interestingly, several studies in patients with dilated cardiomyopathy have failed to show a correlation between MA dilatation and MR.5,32 It is conceivable that reshaping and reorientation of the mitral annulus to the subvalvular apparatus may have been important aspects of the repair. Similarly, the annular dilatation in our experiment was accompanied by displacement of the anterior papillary muscle tip toward the plane of the annulus and may explain the lack of MR that was observed. In this experiment, the results of 1 animal in the EXP group identified the animal as an outlier compared with the remaining EXP group mean values. The MAA in that animal was 3 SDs greater than the EXP group mean value, and 2 + MR was identified with echocardiography. Interestingly, in addition to an increase in the CC dimension, the SL dimension increased by nearly 2 SDs in that animal. Although these observations occurred in 1 animal, there appears to be an upper limit of MAA, beyond which leaflet area is insufficient and MR occurs as has been observed clinically.2 Alternatively, one may speculate that the increased SL dimension and alteration of annular geometry observed in this animal may have been responsible for the MR.

Study Limitations
Certain hemodynamic parameters were different between the CTL and EXP groups that may impact their comparability. The heart rate of the EXP group was slightly, but significantly higher; the heart rates of both groups, however, were in the normal range for sheep. LV pressure values at end systole and PRSW were lower in the EXP group than in the CTL group. Although a lower transvalvular gradient across the mitral valve may have decreased regurgitant flow in the EXP group, there are experimental data that a lower transvalvular gradient decreases one of the forces acting to bring the mitral leaflets into coaptation.3

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References

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