Mechanism of Ischemic Mitral Regurgitation With Segmental Left Ventricular Dysfunction: Three-Dimensional Echocardiographic Studies in Models of Acute and Chronic Progressive Regurgitation

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OBJECTIVES

This study aimed to separate proposed mechanisms for segmental ischemic mitral regurgitation (MR), including left ventricular (LV) dysfunction versus geometric distortion by LV dilation, using models of acute and chronic segmental ischemic LV dysfunction evaluated by three-dimensional (3D) echocardiography.

BACKGROUND

Dysfunction and dilation—both mechanisms with practical therapeutic implications—are difficult to separate in patients.

METHODS

In seven dogs with acute left circumflex (LCX) coronary ligation, LV expansion was initially restricted and then permitted to occur. In seven sheep with LCX branch ligation, LV expansion was also initially limited but became prominent with remodeling over eight weeks. Three-dimensional echo reconstruction quantified mitral apparatus geometry and MR volume.

RESULTS

In the acute model, despite LV dysfunction with ejection fraction \( \leq 23 \pm 8\% \), MR was initially trace with limited LV dilation, but it became moderate with subsequent prominent dilation. In the chronic model, MR was also initially trace, but it became moderate over eight weeks as the LV dilated and changed shape. In both models, the only independent predictor of MR volume was increased tethering distance from the papillary muscles (PMs) to the anterior annulus, especially medial and posterior shift of the ischemic medial PM, measured by 3D reconstruction \((r^2 = 0.75 \text{ and } 0.86, \text{ respectively})\). Mitral regurgitation volume did not correlate with LV ejection fraction or \( \text{dP/dt} \).

CONCLUSIONS

Segmental ischemic LV contractile dysfunction without dilation, even in the PM territory, fails to produce important MR. The development of MR relates strongly to changes in the 3D geometry of the mitral apparatus, with implications for approaches to restore a more favorable configuration. (J Am Coll Cardiol 2001;37:641–8) © 2001 by the American College of Cardiology

Advances in three-dimensional (3D) echocardiography (1–6) can allow us to address uniquely 3D clinical and scientific questions, for example, relating the mechanism of functional mitral regurgitation (MR) in patients with segmental left ventricular (LV) dysfunction to the 3D geometry of the mitral apparatus. Such ischemic MR adversely influences prognosis (7–12), but its mechanism and treatment remain uncertain. Typically, the mitral leaflets are apically displaced, showing incomplete mitral leaflet closure (IMLC) (13,14). Competing explanations for this pattern (15–27) include global LV dysfunction per se, decreasing the ventricular force to close the leaflets (26,27), versus geometric changes in the mitral leaflet attachments due to abnormal motion and distortion of the LV region from which the papillary muscles (PMs) arise (13,14), restricting leaflet closure (18–25). It has been difficult, however, to separate geometric changes from dysfunction in patients and to assess altered 3D geometry from standard two-dimensional (2D) images (28). We therefore proposed to use quantitative 3D echocardiography in animal models to dissociate geometric changes from dysfunction.

Physical principles suggest that little force should be required to close the thin leaflets unless they are abnormally tethered (29). Therefore, we proposed the hypothesis that ischemic LV dysfunction does not produce important MR if LV dilation and associated geometric changes are limited. This was addressed in two complementary models. We first produced acute segmental ischemia in dogs, initially limiting LV expansion by increasing pericardial restraint and decreasing preload, and later permitting LV expansion. We then followed the evolution of MR in a chronic sheep infarct model as the LV progressively remodels over eight weeks (22,23). Both models allow ischemic MR to be analyzed for a constant degree of LV dysfunction but permitting variable LV volume and geometry. Although tethering has been studied in pharmacologically induced...
global LV dysfunction with prominent dilation (30), it has not been studied for segmental dysfunction with less dilation and more localized geometric changes, or related to the spectrum of both acute and chronic infarction as in the current study. Increased understanding of mechanism also has therapeutic implications for improving ways to reverse geometric distortions (9,10,31–34).

METHODS

Acute canine model. Seven mongrel dogs (20 to 28 kg) anesthetized with pentobarbital (30 to 50 mg/kg IV) were intubated and ventilated and underwent left thoracotomy, with Millar catheters placed in the LV and left atrium (LA) and a Transonic flowmeter on the aortic root. After baseline hemodynamic and echo recordings, they were placed on right heart bypass, with a calibrated roller pump controlling cardiac output by pumping filtered and oxygenated venous return from the right atrium into the pulmonary artery. The pericardial space was then reduced by folding the pericardium over itself parallel to the cardiac long axis and suturing.

Chronic sheep model. Seven Dorsett hybrid sheep (30 to 40 kg) anesthetized with thiopental (0.5 ml/kg) were intubated and ventilated with 2% isoflurane and oxygen and given glycopyrrolate (0.4 mg IV) and vancomycin (0.5 g IV). Sterile left thoracotomy was performed, and lidocaine (3 mg/kg IV, then 2 mg/min) was given 10 min before coronary ligation. After baseline imaging, the pericardium was opened and the second and third LCX obtuse marginal branches were ligated (22,23). Imaging was repeated, and the thoracotomy was closed. After eight weeks, each animal had a second thoracotomy under general anesthesia for optimal imaging; 500 ml of 2% triphenyl tetrazolium chloride was then injected, euthanasia induced, and excised hearts were sectioned at 5-mm intervals to measure infarcted and total area by planimeter.

Data collection and analysis. Three-dimensional echo data were acquired using a 5 MHz epicardial multiplane transducer placed at the LV apex (Hewlett-Packard Sonos 2500, Andover, Massachusetts), with special 3D software obtaining 45 rotated images at 4° angular increments with ECG gating, recorded on videotape and magneto-optical disk for analysis on a Silicon Graphics workstation (35). Left ventricle sphericity was determined as actual LV volume divided by that of a sphere with the LV long axis as diameter (18–21). Mitral regurgitation orifice area (MROA) was obtained by Yellin’s method (MROA = (1.1 × RSV) / (0.31 × RT × √mPG)), where MROA = MR orifice area (mm²); RSV = regurgitant stroke volume (ml); RT = regurgitant time/beat (s); and mPG = mean LV–LA pressure gradient (mm Hg) (39,40) and then compared with proximal MR jet cross-sectional area by color Doppler from apical four- and two-chamber view diameters (elliptical area = π × diameter₁ × diameter₂/4) (41,42).

3D PM-mitral relations. The analysis aimed to identify PM displacement relative to the annulus that would increase leaflet tethering, particularly in an abnormal posterior and lateral direction (43,44). As reference frame we took the least-squares plane of the mitral annulus (plane with least deviation of annular hinge points about it) (3). Using this reference, we correlated development of MR with a series of uniquely 3D measurements that cannot be made in any 2D view (Fig. 1). Mitral geometry was analyzed from rotated mid-systolic images (most effective leaflet closure, Fig. 1A) (14,38). The mitral annulus was identified as the leaflet hinge points, confirmed by video review (B, blue points, arrows); the aortic annulus was similarly traced (Fig. 1B, pink points). The PM tips closest to the base of the heart were determined by review of several adjacent images (Fig. 1B, yellow point). The entire set of points (Fig. 1C,D) then established the spatial relations of the mitral valve complex (Fig. 1E,F), including least-squares annular plane, annular centroids and PM tips.

The tethering length over which the mitral leaflets and chordae are stretched between the PMs and the relatively fixed fibrous portion of the annulus (32) was measured as indicated by the arrows in Figure 1F, which views 3D relations from the apex with the annulus en face. These lengths were measured to the medial trigone of the aortic valve (medial junction of aortic and mitral annuli; Fig. 1D-F, red points) because the line connecting this point

Abbreviations and Acronyms

ANOVA = analysis of variance
EF = ejection fraction
IMLC = incomplete mitral leaflet closure
LA = left atrium
LCX = left circumflex coronary artery
LV = left ventricle
MR = mitral regurgitation
MROA = mitral regurgitant orifice area
PM = papillary muscle
3D = three-dimensional
2D = two-dimensional
with the mitral annular centroid roughly bisects the line connecting the PM tips (Fig. 1F). Symmetric outward displacements of the PMs therefore appear symmetric relative to this line (30). Changes in these tethering distances were analyzed as three components: $D_x$ (mediolateral PM shifts), $D_y$ (posterior) and $D_z$ (parallel to the LV long axis). Changes were also measured in the distance between the PM tips, and the angle between the PM-to-annulus distance and the least-squares annular plane (Fig. 1E).

Mitral annular cross-sectional area was measured from the 3D reconstruction at mid-systole (3). In the instrumented acute model, peak transmitral closing force was calculated as peak transmitral pressure gradient times annular area (45).

### Accuracy and reproducibility of 3D echocardiographic measurements

We compared 36 distances measured by 3D echo in the beating canine heart with those measured directly using four sonomicrometer crystals (Sonometrics, London, Canada) placed on the PM tips and at two points on the mitral annulus, as well as 28 distances in a ventricular phantom with crystals, imaged to measure distances by 3D echo reconstruction. In vivo, distances were measured at end-diastole and end-systole at baseline and with phenylephrine infusion and LCX ligation (total = 36). To estimate inter- and intra-observer variability, 18 3D distances from three animals were measured by two independent observers and one observer repeated the measurements later.

### Statistical analysis

Hemodynamic variables, LV volumes and ejection fraction (EF), and mitral valve geometric measures were compared among the stages and animals by two-way analysis of variance (ANOVA) for each model. Significant differences were explored by paired $t$ tests (protected by the Fisher F-test criterion for multiple comparisons). Because of the number of variables studied, the overall ANOVA significance was assessed at the conservative Bonferroni value of $p < 0.005$. Mitral regurgitation stroke volume and orifice area determinants were explored by univariate and stepwise multiple linear regression analysis, entering the absolute value and changes relative to baseline of the 3D measures of mitral attachment geometry (tethering distances for each PM and the sum for both; their x, y and z components and angles relative to the annulus; inter-PM distance and annular area); LV volumes, sphericity index, EF and maximal $dP/dt$; and the calculated transmitial leaflet closure force. Variables were entered as suggested by the regression model F value at $p < 0.05$.

### RESULTS

#### Acute canine model (Tables 1 and 2)

Pericardial restraint and reduced cardiac output initially limited LV volume increases after LCX ligation. With pericardial removal and cardiac output restoration, LV volumes, EF and ejection volume also increased. Mitral regurgitation volume and orifice area did not change from control to LCX ligation with limited dilation, but they increased considerably when the LV was allowed to dilate, with corresponding changes in mitral geometric measures (Table 2), including IMLC area and tethering distances, especially for the ischemic medial PM.
The upper panels of Figure 2 show changes in MR by color Doppler in an apical view, increasing from none at baseline and with LCX ligation and pericardial restraint to moderate with pericardial removal and apical leaflet tenting. Correspondingly, in the lower panels, with LCX ligation but limited LV dilation, the ischemic medial PM was displaced mildly outward (medially and posteriorly); this became prominent with LV dilation, increasing the tethering distance as well as annular area, with mild displacement of the lateral PM as end-systolic volume increased.

Univariate predictors of MR stroke volume and orifice area were the absolute value and its change from baseline of the tethering lengths of both PMs and their mediolateral and posterior (x and y) components, the PM tip separation, mitral annular area, IMLC area, and LV end-diastolic and end-systolic volumes and sphericity indices. Mitral regurgitation stroke volume and orifice area did not significantly correlate with LV EF, maximal LV dp/dt or transmitral leaflet closure force ($r^2$ = 0.01 to 0.10). Multiple linear regression analysis identified the change from baseline in the sum of tethering distances as the only independent factor determining MR stroke volume and orifice area ($r^2$ = 0.75 and 0.83, respectively). Tethering distance and end-systolic sphericity index were correlated ($r^2$ = 0.56). Mitral regurgitation orifice area, which correlated well with proximal jet area by Doppler color flow mapping ($r^2$ = 0.96, SEE = 13 mm$^2$), showed a curvilinear increase with changes in tethering distance ($r^2$ = 0.88, Fig. 3).

**Chronic sheep model (Table 3).** Left ventricular dilation was limited in the acute infarct stage despite decreased EF, but dilation became prominent over eight weeks with maintained EF. Forward aortic stroke volume did not significantly vary among the stages. Mitral regurgitation volume did not significantly change with acute infarction, but it considerably

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### Table 1. Acute Canine Model: Hemodynamic Indices

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Limitation to LV Dilation</th>
<th>No Limitation to LV Dilation</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>116 ± 10</td>
<td>119 ± 17</td>
<td>122 ± 11</td>
<td>n.s.</td>
</tr>
<tr>
<td>Maximum LVP (mm Hg)</td>
<td>105 ± 16</td>
<td>75 ± 17**</td>
<td>81 ± 13*</td>
<td>0.01</td>
</tr>
<tr>
<td>LAP (mm Hg)</td>
<td>6 ± 3</td>
<td>9 ± 4</td>
<td>18 ± 6**‡</td>
<td>0.0001</td>
</tr>
<tr>
<td>LV-LA PG (mm Hg)</td>
<td>99 ± 17</td>
<td>66 ± 17**</td>
<td>63 ± 11**</td>
<td>0.0001</td>
</tr>
<tr>
<td>Peak</td>
<td>61 ± 11</td>
<td>49 ± 11*</td>
<td>35 ± 11‡</td>
<td>0.001</td>
</tr>
<tr>
<td>Closure force (mm Hg cm$^2$)</td>
<td>333 ± 102</td>
<td>216 ± 96**</td>
<td>258 ± 107†</td>
<td>0.003</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/s)</td>
<td>2,370 ± 510</td>
<td>1,530 ± 620**</td>
<td>1,610 ± 310‡</td>
<td>n.s.</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>29.4 ± 5.9</td>
<td>29.7 ± 8.4</td>
<td>52.0 ± 9.4***†</td>
<td>0.0001</td>
</tr>
<tr>
<td>LV ejection volume (ml)</td>
<td>17.1 ± 3.8</td>
<td>23.5 ± 8.8</td>
<td>37.0 ± 8.3***‡</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>42 ± 4</td>
<td>23 ± 8**</td>
<td>29 ± 8†</td>
<td>0.0001</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>12.2 ± 2.4</td>
<td>6.2 ± 0.9**</td>
<td>15.0 ± 4.1†</td>
<td>0.0001</td>
</tr>
<tr>
<td>Aortic stroke volume (ml)</td>
<td>11.9 ± 2.3</td>
<td>5.6 ± 1.1**</td>
<td>8.6 ± 2.6†</td>
<td>0.0001</td>
</tr>
<tr>
<td>MR stroke volume (ml)</td>
<td>0.3 ± 0.5</td>
<td>0.6 ± 0.4</td>
<td>6.4 ± 3.0***‡</td>
<td>0.0001</td>
</tr>
<tr>
<td>MROA (mm$^2$)</td>
<td>0.4 ± 0.7</td>
<td>1.0 ± 0.7</td>
<td>13.6 ± 8.7**‡</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* = $p < 0.05$ relative to control, ** = $p < 0.01$ relative to control, † = $p < 0.05$ relative to the limitation to LV dilation stage, ‡ = $p < 0.01$ relative to the limitation to LV dilation stage.

LAP = left atrial pressure, LV-LA PG = left ventricle to left atrium pressure gradient, LVEDV = left ventricular end-diastolic volume, LVEF = left ventricular end-systolic volume, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, MROA = MR orifice area, HR = heart rate, LVP = left ventricular pressure.

### Table 2. Acute Canine Model: Mitral Valve and Geometric Indices

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Limitation to LV Dilation</th>
<th>No Limitation to LV Dilation</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMLC area (cm$^2$)</td>
<td>-0.07 ± 0.03</td>
<td>0.15 ± 0.29</td>
<td>0.67 ± 0.19**‡</td>
<td>0.0001</td>
</tr>
<tr>
<td>PM-to-annulus tethering distance (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial</td>
<td>27 ± 2</td>
<td>30 ± 3**</td>
<td>33 ± 3**‡</td>
<td>0.0001</td>
</tr>
<tr>
<td>Lateral</td>
<td>26 ± 2</td>
<td>25 ± 3*</td>
<td>28 ± 3**‡</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sum</td>
<td>54 ± 4</td>
<td>55 ± 6</td>
<td>61 ± 5**‡</td>
<td>0.0001</td>
</tr>
<tr>
<td>PM angle (°)</td>
<td>44 ± 9</td>
<td>39 ± 8*</td>
<td>38 ± 8**</td>
<td>(0.01)</td>
</tr>
<tr>
<td>Medial</td>
<td>43 ± 7</td>
<td>46 ± 8</td>
<td>43 ± 9†</td>
<td>n.s.</td>
</tr>
<tr>
<td>Lateral</td>
<td>87 ± 16</td>
<td>85 ± 14</td>
<td>81 ± 19†</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sum</td>
<td>16 ± 2</td>
<td>19 ± 2**</td>
<td>22 ± 2**‡</td>
<td>0.0001</td>
</tr>
<tr>
<td>PM mediolateral separation (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-systolic LV sphericity index</td>
<td>0.23 ± 0.05</td>
<td>0.24 ± 0.08</td>
<td>0.30 ± 0.07**‡</td>
<td>(0.008)</td>
</tr>
<tr>
<td>MA area (cm$^2$)</td>
<td>5.5 ± 1.0</td>
<td>5.2 ± 1.4</td>
<td>6.7 ± 1.4**‡</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* = $p < 0.05$ relative to control, ** = $p < 0.01$ relative to control, † = $p < 0.05$ relative to the limitation to LV dilation stage, ‡ = $p < 0.01$ relative to the limitation to LV dilation stage, IMLC = incomplete mitral leaflet closure, PM = papillary muscle, MA = mitral annular area.
increased in the chronic stage with ventricular remodeling. Mitral geometric changes were mild with acute infarction and prominent in the chronic stage, with ventricular remodeling and increased IMLC area, tethering distance, PM separation, LV sphericity index and annular area.

Triphenyl tetrazolium chloride staining confirmed infarction of the medial PM and adjacent myocardium, involving 20% to 25% (23 ± 2%) of LV myocardial cross-sectional area (23).

The upper panels of Figure 4 show changes in MR by color jet area in an apical view, increasing from none at baseline and trace with acute infarction to moderate at eight weeks, with ventricular dilation and apical leaflet tenting. The lower panels show corresponding geometric changes, with mild outward (medial and posterior) displacement of the ischemic medial PM acutely and more prominent displacement after eight weeks with ventricular remodeling. Annular area (viewed en face) changed only mildly.

Univariate predictors of MR stroke volume were the absolute value and its change from baseline of both PM tethering lengths and their x and y components, the PM tip separation, mitral annular area, IMLC area, and LV end-diastolic and end-systolic volumes and sphericity indices, but not EF. Multiple regression identified the increase in the sum of PM tethering distances as the only independent factor determining MR stroke volume ($r^2 = 0.86$). Tethering distance and its changes were correlated with end-systolic sphericity index ($r^2 = 0.60, 0.64$).

**Figure 2.** Upper panels: Apical two-dimensional echo images (LV on top, LA below the mitral valve, aorta at lower right) showing no mitral regurgitation (MR) at baseline (S1) and with left circumflex coronary artery (LCX) occlusion but pericardial restraint (S2) and moderate MR with the pericardium open (S3). Lower panels: Views of the 3D reconstructions from the apex, with the mitral annulus en face, the PM tips as yellow and green and the anterior annular reference point as red (Fig. 1F). With LCX ligation, the PMs, especially the ischemic medial one (green), migrate away from the annular reference, stretching the leaflets over a larger distance. This shift is mild with limited LV dilation (S1 to S2) and larger when geometric changes are permitted (S3, open pericardium). Other abbreviations as in Figure 1.

**Figure 3.** Correlation between the tethering distance and mitral regurgitation orifice area.

**Figure 4.** The upper panels show changes in MR by color jet area in an apical view, increasing from none at baseline and trace with acute infarction to moderate at eight weeks, with ventricular dilation and apical leaflet tenting. The lower panels show corresponding geometric changes, with mild outward (medial and posterior) displacement of the ischemic medial PM acutely and more prominent displacement after eight weeks with ventricular remodeling. Annular area (viewed en face) changed only mildly.

Univariate predictors of MR stroke volume were the absolute value and its change from baseline of both PM tethering lengths and their x and y components, the PM tip separation, mitral annular area, IMLC area, and LV end-diastolic and end-systolic volumes and sphericity indices, but not EF. Multiple regression identified the increase in the sum of PM tethering distances as the only independent factor determining MR stroke volume ($r^2 = 0.86$). Tethering distance and its changes were correlated with end-systolic sphericity index ($r^2 = 0.60, 0.64$).

**Accuracy of 3D echocardiographic measurements.** Distances between crystals by 3D echo correlated and agreed well with those by sonomicrometry, both in vivo and in vitro ($y = 0.99x + 0.2, r^2 = 0.99, SEE = 0.7\ mm, p = 4 \times 10^{-69}$), with a mean difference of 0.08 ± 0.72 mm (not significant vs. 0). Inter- and intra-observer variability was 0.4 ± 0.9 and 0.2 ± 0.9 mm or 1.5 ± 3.4 and 0.8 ± 3.4%, respectively.

**DISCUSSION**

The results of these studies show that segmental ischemic LV contractile dysfunction fails to produce important MR without LV dilation or distortion. In contrast, MR does develop if the LV is allowed to dilate, with corresponding mitral geometric changes. This is the case in an acute model...
of proximal LCX occlusion in which acute LV dilation can be limited by changing pericardial restraint and preload, as well as in a chronic model of segmental infarction in which acute dilation is limited without additional maneuvers and mitral geometry evolves as the LV remodels. Three-dimensional echo directly confirmed changes in mitral geometry, including an increased tethering distance from the PMs to the anterior annular ring, as well as an increased mitral annular area, with displacements most prominent for the medial PM in the ischemic territory. These changes stretch the leaflets widely over the annulus and restrict their ability to close effectively at the annular level, resulting in apical tenting. The PM tethering length, which most strongly predicts MR, does not appreciably change in a

Table 3. Chronic Sheep Model: Hemodynamic, Left Ventricular and Mitral Valve Indices

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Acute Stage</th>
<th>Chronic Stage</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>95 ± 16</td>
<td>99 ± 18</td>
<td>103 ± 19</td>
<td>n.s.</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>34.2 ± 8.2</td>
<td>41.6 ± 11.8*</td>
<td>68.2 ± 10.5**</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>18.0 ± 5.2</td>
<td>25.5 ± 7**</td>
<td>43.7 ± 8.0†</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>48 ± 4</td>
<td>39 ± 3**</td>
<td>36 ± 7**</td>
<td>0.0001</td>
</tr>
<tr>
<td>LV ejection volume (ml)</td>
<td>16.2 ± 3.2</td>
<td>16.1 ± 5.2</td>
<td>24.5 ± 5.3†</td>
<td>0.002</td>
</tr>
<tr>
<td>Aortic stroke volume (ml)</td>
<td>16 ± 3.7</td>
<td>15.2 ± 4.9</td>
<td>18.5 ± 4.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>MR volume (ml/beat)</td>
<td>0.2 ± 0.7</td>
<td>0.9 ± 0.7</td>
<td>6 ± 2.4†</td>
<td>0.0001</td>
</tr>
<tr>
<td>IMLC area (cm²)</td>
<td>−0.07 ± 0.11</td>
<td>0.02 ± 0.14*</td>
<td>0.46 ± 0.26†</td>
<td>0.0001</td>
</tr>
<tr>
<td>PM to annulus tethering distance (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial</td>
<td>24 ± 1</td>
<td>27 ± 2**</td>
<td>31 ± 4†</td>
<td>0.0001</td>
</tr>
<tr>
<td>Lateral</td>
<td>28 ± 1</td>
<td>28 ± 2</td>
<td>31 ± 2†</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sum</td>
<td>51 ± 2</td>
<td>55 ± 2**</td>
<td>63 ± 4†</td>
<td>0.0001</td>
</tr>
<tr>
<td>PM angle (°)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial</td>
<td>38 ± 8</td>
<td>34 ± 2</td>
<td>31 ± 5*</td>
<td>n.s.</td>
</tr>
<tr>
<td>Lateral</td>
<td>38 ± 4</td>
<td>41 ± 4</td>
<td>37 ± 5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sum</td>
<td>76 ± 10</td>
<td>75 ± 4</td>
<td>68 ± 16‡</td>
<td>0.0001</td>
</tr>
<tr>
<td>PM separation (mm)</td>
<td>19 ± 4</td>
<td>24 ± 4**</td>
<td>30 ± 4†</td>
<td>0.0001</td>
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<tr>
<td>LV Sph (ES)</td>
<td>0.29 ± 0.07</td>
<td>0.38 ± 0.06**</td>
<td>0.47 ± 0.05†</td>
<td>0.0001</td>
</tr>
<tr>
<td>MA area (cm²)</td>
<td>6.5 ± 0.8</td>
<td>6.9 ± 0.9</td>
<td>7.5 ± 0.9**</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* = p < 0.05 relative to control, ** = p < 0.01 relative to control, † = p < 0.01 relative to acute stage, ‡ = p < 0.05 relative to acute stage.

HR = heart rate, LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, IMLC = incomplete mitral leaflet closure, PM = papillary muscle, Sph(ES) = end systolic sphericity index, MA = mitral annulus.

Figure 4. Upper panels: Two-dimensional echo apical four-chamber images in the sheep, with no MR at baseline (left), trace MR acutely after coronary ligation (middle) and apical leaflet tenting with moderate MR in the chronic phase eight weeks later with prominent LV remodeling (right). Lower panels: Views of the 3D reconstructions from the apex (Fig. 1F). With LCX obtuse marginal branches 2 and 3 ligation, the PMs, especially the ischemic medial one (green), migrate away from the annular reference (red), stretching the leaflets over a larger distance. This shift is mild in the acute stage, without LV remodeling, and larger in the chronic stage after remodeling. Other abbreviations as in Figure 1.
direction parallel to the LV long axis, reflecting lack of important acute leaflet-chordal stretch in that direction. Instead, the changes in tethering length relate to mediolateral and posterior PM shifts, redirecting PM tension away from the axial direction that effectively opposes LV force and diverting the leaflets away from closure (43,44).

Of note is that, in both models, tethering length correlated well with LV sphericity index, which, unlike EF, was a univariate predictor of MR severity. This confirms the mechanistic postulate of Sabbah et al. (21) that distortions in LV shape, as opposed to nonspecific increases in volume or decreases in EF, play a central role in displacing the PMs and disrupting coaptation.

The geometric measurements in this study demand the spatial appreciation of 3D echo to recognize the superior tips of the PMs and to provide a consistent reference frame, including the least-squares plane and medial trigone of the mitral annulus. However, it is reasonable to expect that, with appropriate standardization, distances between the PM tips and the contralateral anterior mitral annulus in the apical four- and two-chamber or long-axis views could provide approximate estimates of lateral and medial PM tethering distances, respectively.

These results highlight the importance of the PM tethering distance in determining mitral valve behavior (25). They are consistent with prior studies showing that MR does not result from PM dysfunction alone (16,17,26), but they go beyond those studies to demonstrate that geometric changes are needed for the development of MR with ischemia of the PM territory.

**Study limitations.** Previous 3D echocardiographic study covered only functional MR due to acute global LV dysfunction, with dilation limited by increasing pericardial restraint and decreasing preload (30). The same maneuvers were used in the current acute canine model of segmental ischemia. These maneuvers effectively separate dilation from dysfunction to address mechanism but are not clinically present with unaltered physiology. This limitation, however, is overcome by the chronic sheep model of localized segmental dysfunction, which allows us to analyze the evolution of MR and its determinants without any preload or pericardial alterations.

The clinical spectrum of ischemic MR includes widely varying location, chronicity and severity of LV dysfunction, which cannot entirely be reflected in the models presented; nevertheless, the purpose of this study was specifically to explore models that could separate changes in LV segmental contractile function, present in all infarct stages, from major tethering distance changes present only in the dilated stages and, in such models, to relate MR to 3D mitral geometric changes. This was achieved with models of infero-posterior ischemia resembling the pattern seen in many patients with ischemic MR, for example, due to right coronary artery or LCX lesions (13–15,18,43,44). Moreover, the spectrum of both acute and chronic ischemic changes are represented, with a range of EFs (lower in the canine than the sheep model). Although the chronic stage of the sheep model had lesser decreases in EF (a poor predictor of MR), it had the greatest increases in LV sphericity index (from 0.29 to 0.47), corresponding to the development of MR. This further confirms the crucial role proposed by other investigators for LV shape changes in the mechanism of MR; the prominent LV remodeling in the sheep model leads to PM displacement, increased tethering and MR (18–21).

**Practical implications.** These results are consistent with clinical and experimental observations that regional wall motion abnormality can induce functional MR, of which the primary cause is not the regional dysfunction per se but geometric changes in the LV and mitral valve attachments (13–15,18,43,44). This can also be a consideration in decisions regarding the potential benefit of revascularization in acute inferior infarctions, despite their often limited size (46). Our findings also suggest that surgical approaches could benefit patients by restoring overall mitral valve geometry toward normal. Such maneuvers might include limiting LV size or tethering with increased pericardial restraint, with myoplasty to wrap skeletal muscle around the heart, with infarct plication or posterior wall excision to reduce infarct bulging (47), or with leaflet or chordal elongation. Although annuloplasty ring insertion can limit annular area and improve coaptation, clinical observations suggest that this is not always the case, because of the persistent PM tethering, all of which leads to approaches that combine annuloplasty with infarct reduction to decrease tethering distance (48).

**Conclusions.** In complementary acute and chronic models, segmental infero-posterior myocardial ischemia involving the medial PM without prominent dilation or geometric changes fails to produce important MR. Functional MR relates strongly to changes in the 3D geometry of the mitral valve attachments, with practical implications for approaches to restore a more favorable configuration that reduces or eliminates regurgitation.

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