Annular Versus Subvalvular Approaches to Acute Ischemic Mitral Regurgitation

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Background—Ischemic mitral regurgitation (IMR) has been attributed to annular dilatation, papillary muscle (PM) displacement (“apical leaflet tenting”), or both. We compared the efficacy of reducing annular or subvalvular dimensions to gain more mechanistic insight into acute IMR.

Methods—Eight adult sheep underwent implantation of radiopaque markers on the LV, mitral annulus (MA), each leaflet edge, and each PM tip. Trans-annular septal-lateral (SL) and inter-PM tip sutures were placed and externalized. Biplane videofluoroscopy and transesophageal echocardiography were performed before and continuously during LCx occlusion-induced IMR with SL annular (SLAC) or inter-PM (PAPS) suture tightening (4 to 5 mm of cinching for 5 seconds during ischemia), MA SL dimension, inter-papillary distance (APM-PPM), and the distances between the anterior (APM) and posterior (PPM) PM tips and the mid-septal annulus (“saddle horn”) were calculated from 3-D marker coordinates at end-systole.

Results—SLAC reduced IMR (grade = 2.1 ± 0.6 versus 0.7 ± 0.5, P<0.001), SL annular diameter (4.9 ± 2.5 mm smaller versus precinching; P<0.001), and PM-“saddle horn” distances (0.9 ± 0.7 and 1.0 ± 0.8 mm reduction for APM and PPM, respectively; P<0.005). PAPS reduced APM-PPM distance (3.7 ± 1.8 mm reduction versus precinching; P<0.001), only slightly decreased the PPM-“saddle horn” distance (0.3 ± 0.3 mm reduction; P=0.03), and had no effect on IMR.

Conclusions—Acute IMR was abolished by annular SL reduction, which also repositioned both PM tips closer to the mid-septal annulus and paradoxically increased leaflet “apical tenting”; reducing inter-papillary dimension was not effective, even though it displaced the leaflets toward the annular plane (less “apical tenting”). (Circulation. 2002;106[suppl I]:I-27-I-32.)

Key Words: ischemic mitral regurgitation ■ coronary artery disease ■ mitral regurgitation ■ mitral annulus ■ annular cinching

Suboptimal clinical outcome associated with mitral valve surgery in patients with ischemic mitral regurgitation (IMR)1 have spurred a continued search for better surgical methods. In current clinical practice, ischemic mitral insufficiency is often corrected with ring annuloplasty.2–4 Since valve repair for IMR is preferred to replacement,5,6 new and innovative repair techniques continue to evolve to make repair more predictable and reproducible, and to readdress the shortcomings of annuloplasty rings7 and their non-physiological effects on annular8 and leaflet dynamics.9,10 Recent experimental approaches to IMR have focused on correcting either the annular11,12 or the subvalvular13,14 geometric perturbations associated with IMR, however, the design of better surgical methods to correct IMR is still hindered by incomplete knowledge of the pathophysiology of IMR. Ischemic mitral regurgitation has been attributed to alterations in papillary muscle geometry,15–18 annular dilatation,19 altered left ventricular size and shape,20,21 and depressed LV systolic function,22 but it is not known whether annular or subvalvular changes predominate. Most likely, a combination of factors is culpable in most clinical situations.

Using radiopaque marker technology, we compared the efficacy of reducing annular or subvalvular LV dimensions to gain mechanistic insight into the geometric perturbations responsible for acute ischemic mitral regurgitation.

Methods

Eight adult sheep underwent marker implantation.23 The markers were implanted on the left ventricle, each papillary muscle tip (Figure 1a), around the mitral annulus, and on the central edge of each leaflet (Figure 2). A single 4-0 Prolene suture was anchored with Teflon-felt pledges at the mid-septal annulus (annular “saddle horn”) and externalized through the mid-lateral annulus to a tourniquet on the epicardial surface (“SLAC”, Figure 1a, b). A similar suture placed between the papillary muscle tips was externalized
through the LV wall to a second epicardial tourniquet (“PAPS”, Figure 1a). The papillary muscle suture was placed just below the level of origin of the chordae tendineae on the posterior papillary muscle tip and exteriorized onto the anterior LV wall after being driven through the anterior papillary muscle tip at the same level. The proximal circumflex coronary artery (which is dominant in sheep) was isolated, and a silastic loop was placed proximal to the first obtuse marginal branch for induction of acute posterolateral ischemia and IMR. The animal was weaned from cardiopulmonary bypass and then allowed 5 minutes of recovery; IMR was again induced and data recordings repeated before and during tightening the PAPS suture.

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 to 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 Analysis**

The details of data acquisition, digital transformation, and 3-D reconstruction have been published previously. Two consecutive steady state beats during ischemic mitral regurgitation before and during suture tightening were designated as “Precinching” and “Cinching” data for “SLAC” and “PAPS” in each animal. End-systole (ES) was defined as the frame containing the peak rate of fall of LV pressure (−dP/dt), and end-diastole (ED) as the videofluoroscopic frame containing the peak of the ECG R-wave. Instantaneous LV volume was computed from the epicardial LV markers using a space-filling multiple tetrahedral volume method. MR was graded subjectively by an experienced echocardiographer (D. Liang) according to the extent and width of the TEE color Doppler regurgitant jet and categorized as none (0), mild (+1), moderate (+2), moderate to severe (+3), or severe (+4).

Annular and subvalvular geometry was determined from 3-D coordinates of the implanted markers. The annular septal lateral (SL) diameter was calculated as the distance in three-dimensional space between the 2 markers on the mid-septal and mid-lateral annulus (#1 and #5, respectively; Figure 2); the distance between the anterior (APM) and posterior (PPM) papillary muscle tips was taken as the distance between the respective papillary tip markers. To assess papillary muscle “tethering,” the distance from each papillary muscle tip to the mid-septal annulus (or “saddle horn;” marker #1 Figure 2) was determined. Left ventricular (LV) dimensions and cross sectional area at the mid-ventricular and apical transverse levels were obtained using the respective epicardial LV marker coordinates. Anterior (AML, marker #9 Figure 2) and posterior (PML, marker #10 Figure 2) leaflet edge displacement was defined as the orthogonal distance from each leaflet edge marker to a least squares plane fitted to the annular markers (AML to ACOM Figure 2).

**Statistical Analysis**

All data are reported as mean plus or minus 1 standard deviation (±1 SD) unless otherwise stated. Hemodynamic and marker-derived data from consecutive steady-state beats from each heart were time-aligned at end-diastole. Marker data were calculated over 20 frames before and after end-diastole (sampling rate=60 Hz.), thus allowing evaluation over a time period of 650 ms. The mean and SD for each variable at
TABLE 1. Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Precinching</th>
<th>Cinching</th>
<th>Precinching</th>
<th>Cinching</th>
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<tbody>
<tr>
<td><strong>HR (b/min)</strong></td>
<td>108±9</td>
<td>105±13</td>
<td>106±14</td>
<td>118±11</td>
<td>116±7</td>
</tr>
<tr>
<td><strong>EDP (mm Hg)</strong></td>
<td>10±4</td>
<td>18±8*</td>
<td>19±16</td>
<td>20±7*</td>
<td>20±9</td>
</tr>
<tr>
<td><strong>ESP (mm Hg)</strong></td>
<td>64±14</td>
<td>54±11*</td>
<td>50±17</td>
<td>48±10*</td>
<td>46±11</td>
</tr>
<tr>
<td><strong>LVPrx (mm Hg)</strong></td>
<td>110±9</td>
<td>86±11*</td>
<td>84±15</td>
<td>84±12*</td>
<td>81±15</td>
</tr>
<tr>
<td><strong>EDV (mL)</strong></td>
<td>146±27</td>
<td>180±31*</td>
<td>179±31</td>
<td>178±29*</td>
<td>176±30</td>
</tr>
<tr>
<td><strong>ESV (mL)</strong></td>
<td>108±29</td>
<td>151±37*</td>
<td>150±37</td>
<td>150±36*</td>
<td>150±36</td>
</tr>
<tr>
<td><strong>+dP/dtmax (mm Hg/s)</strong></td>
<td>2418±361</td>
<td>1319±271*</td>
<td>1381±368</td>
<td>1342±314*</td>
<td>1288±372</td>
</tr>
<tr>
<td><strong>MR (0–4)</strong></td>
<td>0.5±0.5</td>
<td>2.1±0.6*</td>
<td>0.7±0.5*</td>
<td>1.8±0.3*</td>
<td>1.5±0.7</td>
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</table>

Control—before circumflex occlusion; SLAC=septal-lateral annular suture (during circumflex occlusion); PAPS=inter-papillary muscle tip suture (during circumflex occlusion); heart rate (HR), end-diastolic pressure (EDP), end-systolic pressure (ESP), peak LV pressure (LVP max), end-diastolic volume (EDV), end-systolic volume (ESV), maximum LV + dP/dt (dP/dt max) and mitral regurgitation (MR).

*P<0.05 versus Control, †P<0.05 versus Precinching by t test for paired observations.

Results

Hemodynamics

Average sheep weight was 64±5 (±1 SD) kg. Mean cardiopulmonary bypass time was 79±8 minute, and the average aortic cross-clamp time was 59±6 minute. Table 1 summarizes the hemodynamic variables in the Control state (before circumflex occlusion) and during acute LV ischemia before and after SLAC and PAPS cinching. IMR before suture tightening in both SLAC and PAPS conditions was associated with significant LV dilatation at end-systole and end-diastole, increased LV end-diastolic pressure, and decreased peak and end-diastolic LV pressure and LV +dP/dt compared with Control. There was no difference in any of the hemodynamic parameters except heart rate between the SLAC and PAPS “precinching” conditions suggesting comparable ischemic insults. During suture cinching there was no change in any hemodynamic parameters. Trace mitral regurgitation was present in these hearts before ischemia (Table 1), which increased to moderate IMR during LV ischemia before both SLAC and PAPS suture tightening. The MR jet by TEE was mainly central and holosystolic. IMR was almost completely abolished by cinching of the SLAC suture, but unaffected by PAPS tightening.

Annular and Subvalvular Geometry

Neither SLAC nor PAPS cinching induced major changes in LV short axis dimensions or cross sectional areas (Table 2), although slight dilatation of the apical LV transverse region was observed with SLAC. Table 3 presents end-systolic annular and subvalvular distances before and during SLAC and PAPS suture tightening. Significant changes in annular and subvalvular distances because of suture cinching are shown diagrammatically in Figure 3. SLAC cinching, as expected, substantially reduced the annular septal-lateral dimension but also repositioned both papillary muscle tips closer to the annular “saddle horn” and unexpectedly resulted in displacement of both mitral leaflet edge markers away from the annular plane. Conversely, reduction of inter-papillary distance by PAPS cinching was associated with displacement of leaflet edges toward the mitral annular plane, and minimal repositioning of the posterior papillary muscle tip toward the annular “saddle horn”. The reduction in the distance between each papillary muscle tip and the mid-septal annulus was larger with SLAC compared with PAPS throughout the entire cardiac cycle (Figure 4). In summary, SLAC tightening resulted in significant annular and subvalvular geometric alterations while PAPS cinching affected mainly subvalvular geometry.

TABLE 2. Ventricular Dimensions at End-Systole

<table>
<thead>
<tr>
<th></th>
<th>SLAC</th>
<th>Cinching</th>
<th>PAPS</th>
<th>Cinching</th>
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<tbody>
<tr>
<td><strong>Mid-Ventricle</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SL (mm)</td>
<td>56.2±8.6</td>
<td>56.7±8.4</td>
<td>55.8±8.0</td>
<td>56.0±8.4</td>
</tr>
<tr>
<td>AP (mm)</td>
<td>67.8±5.9</td>
<td>68.7±6.0</td>
<td>68.1±5.5</td>
<td>67.7±5.5</td>
</tr>
<tr>
<td>Area (cm²)</td>
<td>19.4±3.3</td>
<td>18.9±3.0</td>
<td>18.9±3.0</td>
<td>18.9±3.1</td>
</tr>
<tr>
<td><strong>Apical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SL (mm)</td>
<td>52.1±4.8</td>
<td>52.6±4.7</td>
<td>51.7±4.5</td>
<td>51.8±4.3</td>
</tr>
<tr>
<td>AP (mm)</td>
<td>47.7±1.7</td>
<td>48.2±2.0*</td>
<td>47.8±2.1</td>
<td>46.8±1.6</td>
</tr>
<tr>
<td>Area (cm²)</td>
<td>11.4±1.7</td>
<td>11.6±1.7*</td>
<td>11.4±1.7</td>
<td>11.3±1.7</td>
</tr>
</tbody>
</table>

SLAC=septal-lateral annular suture; PAPS=inter-papillary muscle tip suture; SL=septal lateral; AP=anterior-posterior; Area=cross sectional LV area. *P<0.05 versus Precinching by t test for paired observations.
TABLE 3. Annular and Subvalvular Geometry at End-Systole

<table>
<thead>
<tr>
<th></th>
<th>Precinching</th>
<th>Cinching</th>
<th>Precinching</th>
<th>Cinching</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLₘₐₜ (mm)</td>
<td>27.8±2.1</td>
<td>22.9±3.2*</td>
<td>29.7±2.7</td>
<td>30.2±2.6*</td>
</tr>
<tr>
<td>APM-PPM (mm)</td>
<td>35.7±1.4</td>
<td>36.5±1.1*</td>
<td>34.7±1.4</td>
<td>31.0±1.8*</td>
</tr>
<tr>
<td>APM-Saddle horn (mm)</td>
<td>49.1±3.5</td>
<td>48.2±3.2*</td>
<td>49.3±3.2</td>
<td>49.3±3.3</td>
</tr>
<tr>
<td>PPM-Saddle horn (mm)</td>
<td>52.3±3.8</td>
<td>51.3±3.6*</td>
<td>52.7±3.7</td>
<td>52.4±3.6*</td>
</tr>
<tr>
<td>AML-MA Plane (mm)</td>
<td>6.8±1.3</td>
<td>7.3±1.3*</td>
<td>6.6±1.3</td>
<td>6.1±1.2*</td>
</tr>
<tr>
<td>PML-MA Plane (mm)</td>
<td>7.4±1.5</td>
<td>7.8±1.4*</td>
<td>7.3±1.7</td>
<td>6.8±1.7*</td>
</tr>
</tbody>
</table>

SLAC = septal-lateral annular sutures; PAPS = inter-papillary muscle tip sutures; SLₘₐₜ = mitral annular septal-lateral dimension; APM-PPM = distance between anterior (APM) and posterior (PPM) papillary muscle tips; APM-saddle horn = distance from the anterior papillary muscle tip to the mid-septal annulus; PPM-saddle horn = distance from the posterior papillary muscle tip to the mid-septal annulus; AML-MA plane = distance from the anterior (AML) leaflet edge marker to the mitral annular plane; PML-MA plane = distance from the posterior (PML) leaflet edge marker to the mitral annular plane. *P<0.05 versus Precinching by t test for paired observations.

Discussion

Mitril reparative techniques continue to evolve, but ischemic mitral regurgitation remains a challenging clinical problem for which a reproducible and reliable surgical correction is yet to be found. Ring annuloplasty, leaflet extension, leaflet approximation, papillary muscle translocation, and subvalvular interventions aimed at correcting leaflet tethering have been introduced as surgical options for the treatment of IMR. In this experiment, we compared the efficacy of reducing annular or subvalvular LV dimensions in correcting acute IMR and found that annular septal-lateral diameter reduction almost completely abolished IMR, while reducing inter-papillary distance had no effect. Paradoxically, reducing IMR using SLAC was associated with apical displacement of the leaflet edges, while IMR persisted when the leaflets were brought closer to the annular plane by PAPS cinching.

Annular reduction with an annuloplasty ring is thought to treat IMR due mainly to septal-lateral mitral annular diameter reduction, as this is the principal direction of annular dilatation during posterolateral LV ischemia; therefore, it is not unexpected that isolated annular reduction with SLAC suture tightening would diminish IMR. It is important, however, to emphasize that annular SL reduction was also associated with repositioning of both papillary muscles closer to the mid-septal annulus. This “tethering” distance has been found in experimental and clinical studies to be an independent predictor of regurgitant volume. It probably was a combination of annular and subvalvular alterations that resulted in the efficacy of the SLAC suture. These data suggest that annular interventions also alter subvalvular geometry, which corroborates previous ovine experiments which found that ring annuloplasty prevents posterior leaflet restriction and anterior leaflet extension during acute ischemia, suggesting an effect on the subvalvular apparatus. The concept of annular and ventricular remodeling with an undersized annuloplasty ring to treat patients with functional mitral regurgitation further supports these findings. It appears that with SLAC cinching not only the annulus but also the entire lateral LV wall is repositioned, although no significant changes in short axis LV dimensions at the mid-ventricular and apical LV levels were observed. These subvalvular alterations may be expected to be more pronounced with ring annuloplasty, as rings reduce the mitral annulus to a greater extent than does SLAC suture cinching.

During SLAC cinching, both leaflet edge makers became displaced more apically; although these unexpected changes were very small (less than 1 mm), they were consistent. We conjecture that SLAC cinching permitted apical displacement of leaflet edges while abolishing IMR by increasing leaflet coap-

Figure 3. Group mean data for changes in annular and subvalvular distances (in mm, dashed lines) resulting from SLAC (left panel) or PAPS (right panel) suture tightening. +Δ = increase in distance; −Δ = decrease in distance; SL = annular septal-lateral dimension; AML = anterior mitral leaflet; PML = posterior mitral leaflet; AV = aortic valve; NC = no change; only significant changes in distances (mean±SD, P<0.05) with suture cinching are shown.
tation as the direction of annular reduction was orthogonal to the line of leaflet coaptation. On the other hand, reduction of inter-papillary distance during IMR reduced leaflet “tenting” and both leaflet edge makers were brought closer to the annular plane; however, this reduction in leaflet “tenting” surprisingly did not translate into less IMR, as apical leaflet displacement is a cause of IMR. On the other hand, PAPS cinching did not decrease annular size; therefore, it is likely that although less leaflet restriction was present, leaflet coaptation area remained insufficient because of persistent annular dilatation, as observed in an ovine model of functional MR.37

In the current experiment, development of IMR was associated with significant increases in end-diastolic and end-systolic LV volumes; however, no change in LV volume accompanied the elimination of IMR during SLAC, nor did SLAC tightening decrease any LV short axis dimensions or cross sectional areas. Although alterations in LV shape have been implicated in the pathogenesis of IMR, device-based alterations in LV size and shape have been shown to have little effect on MR associated with dilated ventricles in experimental or clinical studies. Thus, at least in this model of ovine acute posterolateral LV ischemia, it appears that interventions aimed at normalizing ventricular chamber size and geometry are not necessary to treat acute IMR effectively. Increased inter-papillary muscle distance has also been observed in association with experimental and clinical IMR but its contribution to the pathogenesis of IMR, beyond being a marker of LV chamber dilatation, is unclear. Although inter-papillary muscle distance was reduced by PAPS cinching, the posterior papillary muscle tip was only slightly repositioned toward the annular “saddle horn.” Experimental data from ovine studies suggests that repositioning of the posterior papillary muscle toward the mid-anterior septal annulus is paramount to abolish IMR. Thus, it may be that subvalvular interventions should be aimed more specifically at reducing this “tethering” distance. On the other hand, the goal of papillary muscle repositioning is to reduce apical tethering of the mitral leaflets, which was observed during PAPS cinching; but, paradoxically, this had no effect on IMR.

These observations indicate that annular reduction was more effective than inter-papillary cinching in treating acute IMR in sheep; however, suture reduction of the annular septal-lateral dimension was associated with significantly repositioning both papillary muscle tips indicating an influence on the subvalvular mitral apparatus. It is fair to conclude, therefore, that SLAC abolished acute ovine IMR by virtue of a combination of annular as well as subvalvular effects. New surgical mitral reparative procedures aimed at correcting IMR should strive to correct both annular and subvalvular geometric perturbations.

**Study Limitations**

The results of this experiment must be interpreted in light of limitations which preclude direct extrapolation of these observations to the clinical setting. Ovine acute IMR does not reflect the clinical entity where LV remodeling and chamber dilatation may have a predominant effect on the pathogenesis of IMR. This acute IMR model, however, can serve as a research tool to learn more about the 3-D valvular and subvalvular perturbations which cause IMR. The observed changes in annular and subvalvular distances were very consistent but quite small, being sub-millimeter changes in some instances. Conversely, acute IMR in the same animal model results from very small perturbations in the valvular apparatus, therefore, these geometric

![Figure 4. Group mean data for the distance from anterior (APM; top panel) and posterior (PPM; bottom panel) papillary muscle tip to the annular “saddle horn” before (solid squares) and during (open squares) cinching of the SLAC (left) or PAPS (right) sutures during posterolateral ischemia. A 650 ms time interval centered at end-diastole (t=0) is illustrated for both groups.](http://circ.ahajournals.org/)
alterations observed with suture cinching most likely represent clinically relevant changes. The myocardial marker method requires suturing small metal markers to intra-cardiac structures, but echocardiographic studies suggest that the markers do not interfere with mitral annular or leaflet motion as they are very small (aggregate mass = 20 ± 6 mg). The MR was graded qualitatively using standard clinical criteria rather than as quantitative regurgitant volume, but estimation of regurgitant volume or effective regurgitant orifice (or “ERO”) using echocardiography relies on many assumptions which can introduce error. Despite the limitations inherent in this particular experimental preparation, reliable models of cardiac pathophysiology have been established in similar ovine models.

Acknowledgments

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References

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