Geometric Distortions of the Mitral Valvular-Ventricular Complex in Chronic Ischemic Mitral Regurgitation

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Background—Better understanding of the precise 3-dimensional geometric changes of the mitral valvular-ventricular complex in chronic ischemic mitral regurgitation (CIMR) is needed in order to devise better surgical repair techniques. We hypothesized that changes after inferior myocardial infarction would be different in hearts that developed CIMR compared with those that did not.

Methods and Results—Twenty-four sheep underwent coronary snare and marker placement (annulus, papillary muscles, and anterior and posterior leaflets). After 8 days, cinefluoroscopy provided 3-dimensional marker data, and snare occlusion of obtuse marginal branches created inferior myocardial infarction, including the posterior papillary muscle. After 7 weeks, the 16 surviving animals were studied again and grouped by mitral regurgitation grade (≥ 2+, n=10 versus ≤ 1+, n=6). End-systolic mitral annulus dimensions, components of papillary muscle and leaflet displacement, were calculated. After inferior myocardial infarction, total displacement of the posterior papillary muscle from the midseptal annulus (“saddle horn”) was greater in CIMR(+): 6.5±3.2 versus 3.1±2.7 (P=0.02), with the posterior papillary muscle moving more laterally (6.8±3.4 versus 2.5±3.5 mm, P=0.01). Increase in mitral annular septal-lateral diameter was greater in animals with CIMR (4.9±2.7 versus 2.3±2.0, P=0.02), and apical displacement of the posterior leaflet (PL) margin was also greater in the CIMR(+) group (1.7±1.0 versus 0.3±0.5, P=0.01).

Conclusions—The CIMR(+) group had greater septal-lateral annular dilatation, lateral posterior papillary muscle displacement, and apical PL restriction, indicating that these associated geometric alterations may be important in the pathogenesis of CIMR. Treatment of CIMR should address both annular septal-lateral dilatation and lateral displacement of the posterior papillary muscle. (Circulation. 2003;108[Suppl II]:II-116-II-121.)

Key Words: mitral regurgitation ▪ ischemic mitral regurgitation ▪ mitral annuloplasty ▪ mitral valve repair ▪ myocardial ischemia ▪ ischemic heart disease

Ischemic mitral regurgitation is a common and important complication after myocardial infarction, associated with excess mortality independent of underlying left ventricular dysfunction. Ring annuloplasty, the standard surgical treatment for CIMR, has frustratingly variable results and can be associated with residual or recurrent mitral regurgitation (MR), which is found in upwards of 30% of patients and is associated with a poor prognosis. Subvalvular adjuncts to ring annuloplasty for CIMR have been proposed, but quantitative 3-dimensional analysis of the perturbations of the valvular-ventricular complex associated with CIMR is required for rational design of improved repair methods. The purpose of this study was to gain mechanistic insight into the pathogenesis of CIMR by examining the distortions of the mitral valvular-ventricular apparatus in an ovine model of chronic infarction. We hypothesized that the geometrical changes in the mitral valvular-ventricular complex after inferior myocardial infarction would be different in animals that developed CIMR compared with those that did not. Elucidating the differences in anatomic remodeling between animals with and without CIMR after a similar ischemic insult should provide mechanistic insights into the key perturbations that render the mitral valve incompetent after inferior myocardial infarction.

Methods

Surgical Preparation

Twenty-four Dorsett hybrid sheep (71±5 kg) were premedicated with ketamine (25 mg/kg i.m.), and anesthesia was induced with sodium thiopental (6.8 mg/kg i.v.) and maintained with inhalational isoflurane (1–2.5%). Through a left thoracotomy, 8 tantalum myocardial markers (#13–20; Figure 1) were inserted in the left ventricular epicardial layer along 4 equally spaced longitudinal meridians. Prolene 2 to 0 sutures were passed loosely around the 1, 2, or occasionally 3 obtuse marginal branches of the left circumflex...
coronary artery located between the posterior vein of the left ventricle and the middle cardiac vein, and loosely snared using the method of Llaneras et al. After establishment of cardiopulmonary bypass, tantalum markers were placed at the tips of both the anterior and posterior papillary muscles (A10 and A11), and 8 markers were sutured around the circumference of the mitral annulus (1 near each commissure (A2, A6) and 3 along the septal, clinically termed “anterior” (A0, A1, A7), and lateral, clinically termed “posterior,” (A3, A4, A5) annulus (Figure 1). Miniature gold markers were sutured at the central edge of the anterior (#8) and posterior (#9) leaflets. A micromanometer pressure transducer (PA4.5-X6; Konigsberg Instruments, Inc.) was placed in the left ventricular chamber through the apex.

**Experimental Protocol**

After 8±2 days, each animal was taken to the cardiac catheterization laboratory, sedated with ketamine (1–4 mg/kg i.v. infusion) and diazepam (5 mg i.v. bolus as needed), intubated, mechanically ventilated, and maintained with inhalational isoflurane (1–2.5%). Transeosophageal echocardiography and coronary angiography were performed, and baseline videofluoroscopic marker and hemodynamic data acquired.

After premedication with lidocaine (100 mg i.v.), bretylium (75 mg i.v.), and magnesium (3 g i.v.), the coronary artery snare was then tightened, and complete occlusion of the selected vessels verified by angiography. An epinephrine drip was titrated to maintain coronary perfusion pressure (aortic diastolic pressure minus left ventricular diastolic pressure) >60 mmHg. Ventricular arrhythmias were treated with lidocaine (50–100 mg i.v.) and amiodarone (50–150 mg i.v.), as needed. The animal was then stabilized and recovered. The animals were followed for clinical signs of heart failure (tachypnea, lethargy, and anorexia), and serial transthoracic echocardiography was used to detect myocardial volume is included in calculation of left ventricular volume, relative changes in left ventricular chamber size are accurately reflected.

**Papillary Muscle Geometry**

End-systolic papillary muscle positions were determined using a reference system (Figure 1) defined by the least-squares best-fit plane of the annular markers, with the origin at the projection of the mid-septal annulus (“fibrosa” or saddle horn) marker (0) on this plane, positive lateral axis (L’) in the annular plane passing through the mid-lateral annulus marker (#4), positive posterior axis (P’) in the annular plane directed toward the right fibrous trigone, and positive apical axis (A’) normal to the annular plane and directed toward the left ventricular apex. The total end-systolic papillary tip displacements between the baseline and chronic conditions were resolved into their lateral, posterior, and apical components (L, P, and A, respectively).

**Mitral Leaflet Geometry**

End-systolic anterior and posterior leaflet edge positions were calculated as the distance from the leaflet edge markers to the annular plane, with end-systolic leaflet displacements being the change in this distance between baseline and chronic studies. Leaflet displacements between baseline and chronic conditions were also resolved into their lateral, posterior, and apical components (L, P, and A).

**Mitral Annular Geometry**

The septal-lateral diameter of the annulus was calculated as the distance in 3-dimensional space between the 2 markers placed in the middle of
the septal and lateral mitral annulus, respectively (A0 and 4, Figure 1). The commissure-commissure diameter was calculated as the distance between the 2 annular commissural markers (#2 and 6, Figure 1).

**Statistical Analysis**

All of the data are reported as mean ± SD. Changes in the CIMR(+) and CIMR(−) groups from baseline to chronic were analyzed using Student’s t test for paired comparisons. Changes from baseline to chronic conditions between the CIMR(+) and CIMR(−) groups were compared using a t test for unpaired comparisons.

**Results**

Table 1 summarizes hemodynamic data from the CIMR(+) and CIMR(−) groups at baseline and after chronic infarction. Left ventricular dP/dt fell, and end-diastolic volume index (ESVI) and end-diastolic volume index (EDVI) rose in both groups, whereas the CIMR(+) animals also had an increase in LVEDP and severity of MR. There were no statistically significant differences between the CIMR(+) and CIMR(−) groups at baseline with regard to hemodynamics or annular, subvalvular, or leaflet geometry.

Table 2 and Figures 2 and 3 summarize mitral annular dimensions at end-systole. Both groups developed annular dilatation, with the increase in septal-lateral dimension being greater in the CIMR(+) group than in the CIMR(−) group (4.9±2.7 versus 2.3±2.0, P=0.02). The amount of commissure-commissure annular dilatation after inferior MI was not statistically different between the 2 groups.

Table 2, and Figures 2 and 3 summarize papillary muscle displacements after infarction. The increase in total distance from the posterior papillary muscle tip to the fibrosa was greater in the CIMR(+) animals than in the CIMR(−) animals (6.5±3.2 versus 3.1±2.7, P=0.02), and was associated with greater lateral displacement of the posterior papillary muscle (PPM; 6.8±3.4 versus 2.5±3.5 mm, P=0.01). In both groups, the anterior papillary muscle moved toward the apex, and the PPM was displaced toward the annulus in the left ventricular long axis dimension.

Table 3, and Figures 2 and 3 present anterior and posterior mitral leaflet positions at end-systole before and after chronic infarction. No significant changes in anterior leaflet edge position were noted in the CIMR(−) group. In the CIMR(+) hearts, the anterior leaflet moved 2.5±1.8 mm laterally, but the posterior leaflet moved 4.4±3.2 laterally, 1.2±1.5 mm

**Table 1. Hemodynamics and Mitral Regurgitation**

<table>
<thead>
<tr>
<th></th>
<th>CIMR(−)</th>
<th></th>
<th>P</th>
<th>CIMR(+)</th>
<th></th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Chronic</td>
<td></td>
<td>Baseline</td>
<td>Chronic</td>
<td></td>
</tr>
<tr>
<td>HR (min⁻¹)</td>
<td>103±14</td>
<td>114±7</td>
<td>0.48</td>
<td>108±18</td>
<td>99±14</td>
<td>0.06</td>
</tr>
<tr>
<td>LV dP/dt max (mm Hg/s)</td>
<td>1921±400</td>
<td>1604±512*</td>
<td>0.004</td>
<td>1979±785</td>
<td>1256±506*</td>
<td>0.002</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>18±4</td>
<td>20±4</td>
<td>0.08</td>
<td>17±4</td>
<td>21±4*</td>
<td>0.01</td>
</tr>
<tr>
<td>EDVI (ml/M²)</td>
<td>71±11</td>
<td>83±16*</td>
<td>0.02</td>
<td>64±18</td>
<td>90±20*†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESVI (ml/M²)</td>
<td>56±12</td>
<td>67±14*</td>
<td>0.01</td>
<td>50±16</td>
<td>69±15†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MR (4−4+)</td>
<td>0.6±0.2</td>
<td>0.9±0.2</td>
<td>0.05</td>
<td>0.6±0.5</td>
<td>2.5±0.6*</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*P<0.05 vs. baseline.
†P<0.025 change from baseline in CIMR(+) vs. change from baseline in CIMR(−) group.

HR=heart rate; LV dP/dt max=maximum of first derivative of pressure versus time; LVP max=maximum LV pressure; LVEDP=LV pressure at end-diastole; EDV=end-diastolic volume; ESV=LV end-systolic volume; MR=mitral regurgitation.

**Table 2. Mitral Annular and Papillary Muscle Displacements**

<table>
<thead>
<tr>
<th></th>
<th>CIMR(−)</th>
<th></th>
<th>P</th>
<th>CIMR(+)</th>
<th></th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Chronic</td>
<td></td>
<td>Baseline</td>
<td>Chronic</td>
<td></td>
</tr>
<tr>
<td>Annular S-L (mm)</td>
<td>31.9±4.7</td>
<td>34.3±5.3*</td>
<td>0.03</td>
<td>28.5±2.3</td>
<td>33.4±4.2†</td>
<td>0.0003</td>
</tr>
<tr>
<td>Annular C-C (mm)</td>
<td>35.2±5.6</td>
<td>39.0±5.8*</td>
<td>0.01</td>
<td>35.3±2.9</td>
<td>40.6±3.6*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PPM to fibrosa (mm)</td>
<td>50.2±4.7</td>
<td>53.1±4.6*</td>
<td>0.01</td>
<td>48.9±5.1</td>
<td>53.1±5.8*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>APM to fibrosa (mm)</td>
<td>50.1±4.3</td>
<td>53.2±5.2*</td>
<td>0.016</td>
<td>51.6±8.8</td>
<td>58.1±1.0*†</td>
<td>0.0001</td>
</tr>
<tr>
<td>APM posterior (mm)</td>
<td>−15.5±8.2</td>
<td>−15.4±7.1</td>
<td>0.86</td>
<td>−17.6±5.4</td>
<td>−19.9±6.5</td>
<td>0.05</td>
</tr>
<tr>
<td>PPM posterior (mm)</td>
<td>6.2±6.8</td>
<td>14.4±5.3*</td>
<td>0.02</td>
<td>6.0±6.7</td>
<td>14.1±6.8*</td>
<td>0.001</td>
</tr>
<tr>
<td>APM lateral (mm)</td>
<td>29.1±9.8</td>
<td>30.9±11.6</td>
<td>0.11</td>
<td>25.9±6.1</td>
<td>28.8±6.5*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PPM lateral (mm)</td>
<td>31.5±3.0</td>
<td>34.0±5.4</td>
<td>0.15</td>
<td>32.1±6.4</td>
<td>38.9±8.7†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>APM apical (mm)</td>
<td>35.0±8.9</td>
<td>36.1±9.0*</td>
<td>0.002</td>
<td>35.6±5.1</td>
<td>36.6±4.7*</td>
<td>0.007</td>
</tr>
<tr>
<td>PPM apical (mm)</td>
<td>36.1±3.8</td>
<td>34.8±3.9*</td>
<td>0.002</td>
<td>34.1±4.5</td>
<td>31.5±4.9*</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*P<0.05 vs. Baseline.
†P<0.025 change from baseline in CIMR(+) vs. change from baseline in CIMR(−) group.

S-L=mitral annular septal-lateral dimension; C-C=mitral annular commissure-commissure dimension; APM to fibrosa=total 3-D distance from mid-septal annulus to anterior papillary muscle tip; PPM to fibrosa=total 3-D distance from mid-septal annulus to posterior papillary muscle tip.
posteriorly, and 1.7±1.0 apically. In addition, the apical displacement of the posterior leaflet was significantly greater than the change in the CIMR(−) hearts (1.7±1.0 versus 0.3±0.5, \(P=0.01\)).

**Discussion**

This study provides novel insight into the pathogenesis of CIMR in 3 ways: (1) comparison of the mitral valve geometry of the CIMR(+) animals against both their own baseline geometry and a negative control group of CIMR(−) animals that suffered a similar inferior MI, yet did not develop important mitral incompetence; (2) complete characterization of the alterations in papillary muscle 3-dimensional geometry after chronic infarction; and (3) description of the 3-dimensional geometric perturbations of specific loci in the individual mitral leaflets after infarction.

The results of this experiment resemble the clinical situation where only some patients develop CIMR after inferior MI. The surgically-created infarction caused similar and substantial hemodynamic and geometric perturbations in both groups, but those in the CIMR(−) hearts were not sufficient to produce CIMR. By comparing the changes in the animals that developed CIMR with the changes in those that did not, we could examine which specific distortions render the valve incompetent after chronic infarction.

**Annular Geometry**

Chronic infarction caused marked increases in mitral annular dimensions in both groups, with the increase in septal-lateral dimension being significantly greater in animals with CIMR. Septal-lateral diameter is often implicated in leaflet maladaptation in acute ischemic MR and functional MR or CIMR, whereas the mechanistic importance of commissure-to-commissure annular dilatation has been debated. Green et al used topical phenol to create mitral annular dilation in the commissure-commissure (but not septal-lateral) direction without MR. Commissure-commissure annular dilatation was similar in the CIMR(+) and CIMR(−) animals, suggesting that remodeling in this dimension is not sufficient to produce functional MR. These increases in annular dimensions require the mitral leaflets to cover more area, exhausting the normal excess “reserve” of leaflet tissue, which is additionally compounded by less effective leaflet closure because of apical tethering or tenting of the leaflets.

**Papillary Muscle Geometry**

Previous clinical and experimental studies have described the role of papillary muscle displacement in the development in CIMR. Other investigators have used echocardiography to link both total and laterally-directed papillary muscle displacement to apical restriction of the mitral leaflets. This study is the first to characterize fully the 3-dimensional geometry of the papillary muscles in the setting of CIMR, which might be expected to produce greater remodeling of the subvalvular apparatus. This enables the determination of not only how much, but in which direction each papillary muscle was displaced after MI. In the present study, infarction caused the posterior papillary muscle to move posteriorly and “upwards” toward the annulus in both groups, whereas a 6.8 mm lateral displacement of the posterior papillary muscle only in the CIMR(+) hearts accounted for a 7-mm increase in total PPM displacement from the fibrosa. The upward movement of the PPM in the long axis,
a previously unreported finding, is consistent with previous studies of acute ischemic MR,7,21 and paradoxically should theoretically tend to relieve apical tenting of the mitral leaflets. This displacement of the posterior papillary muscle tip closer to the annulus probably results from both a failure of the ischemic posterior papillary muscle to contract during systole (as described by Messas et al22) and lengthening of the infarcted papillary muscle over time. However, the posterior and lateral movement of the posterior papillary muscle was great enough to cause net total posterior papillary muscle displacement resulting in apical leaflet restriction. As PPM displacement in the apical and posterior directions was similar in both groups, we believe that the additional lateral PPM displacement, which was significantly greater in the CIMR(+) hearts than the CIMR(−) hearts (6.8±3.4 versus 2.5±3.5 mm, P=0.01), was a dominant factor in the development of CIMR after inferior myocardial infarction in this model, as shown in Figure 3.

The nonischemic anterior papillary muscle may also play a role in apical leaflet restriction.6,17,21 In this study, the normally shortening anterior papillary muscle was apically displaced at end-systole relative to baseline in both the CIMR(+) and CIMR(−) groups.

**Leaflet Geometry**

Consistent with the 3-dimensional displacements of the papillary muscles, CIMR was associated with apical restriction of the posterior leaflet, which was not seen in the CIMR(−) group. Such apical displacement of the leaflet (Carpentier type IIIb restricted systolic leaflet motion) prevents effective valve closure.23 Leaflet restriction, measured echocardiographically as apical displacement of the point of coaptation of both mitral leaflets, correlated with posterior and lateral papillary muscle displacement,17,20 but the present findings underscore the importance of examining alterations in 3-dimensional papillary muscle geometry as a mechanism of CIMR. In the present experiment, which uniquely allowed independent assessment of the position of each leaflet edge, the anterior leaflet was not displaced apically after infarction, although with more time and additional remodeling (beyond 7 weeks), apical restriction of the anterior leaflet (AL) might occur. CIMR was also associated with posterior leaflet displacement in the posterior direction, and lateral displacement of both leaflets. In an ovine model of acute IMR, Lai et al demonstrated similar lateral displacement of the central scallop of the posterior leaflet, suggesting that inter-scallop malcoaptation could be a mechanism of MR.23 The CIMR(−) animals did not have any changes in end-systolic leaflet position after inferior myocardial infarction.

**Summary**

In this study of the 3-dimensional geometric distortions of the mitral apparatus after inferior MI, sheep that developed CIMR demonstrated greater PPM displacement (particularly lateral movement of the posterior papillary muscle), septal-lateral annular dilatation, and apical restriction of the posterior leaflet than animals that did not develop CIMR. The combination of these specific valvular and subvalvular displacements was sufficient to create leaflet malcoaptation and CIMR. This insight into the 3-dimensional perturbations of mitral valvular geometry in CIMR should help guide the more rational design of new adjunctive surgical reparative techniques for this frustrating surgical problem, as failure to address the subvalvular changes may contribute to the variability of results and recurrence of CIMR after ring annuloplasty, which only deals with annular dilatation. Our experimental findings indicate that repair strategies that address both the subvalvular6,7 and the annular changes, specifically septal-lateral annular dilatation and lateral displacement of the PPM, are needed.

**Study Limitations**

This study used a model of ovine chronic inferior infarction that differs from the clinical entity in some respects. The sheep have all undergone opening of the pericardium, cardiopulmonary bypass, and surgical manipulation of the mitral apparatus. Also, differences in leaflet, annular, papillary muscle, and coronary anatomy between sheep and humans may influence the anatomical remodeling in chronic infarction and the distortions required to develop CIMR.

Baseline differences between the CIMR(+) and CIMR(−) groups might account for the development of CIMR in some sheep but not in others. However, no significant differences in baseline geometry or hemodynamics were demonstrable between the 2 groups. Furthermore, comparison of the geometric changes in the 2 groups after normalization for body surface area and baseline EDV yielded significant differences
only in the same parameters as the initial analysis. Furthermore, the CIMR(+) and CIMR(−) groups were not different with respect to infarct location or the number of vessels ligated. A more detailed analysis to identify why CIMR develops in some animals but not others is currently underway in additional animals.

Quantitative measures of MR, such as estimated regurgitant orifice and regurgitant volume, have shown promise in studies of CIMR. In this experiment, severity of MR was graded semiquantitatively and subjectively by jet size on a scale of 0 to 4+ (a standard method used in clinical practice) by the same echocardiographer (DL). Increased separation between the esophagus and the heart in sheep relative to humans resulted in variable echocardiographic image quality, precluding the calculation of more quantitative measures of MR.

Leaflet geometry in this study was characterized by markers placed on the central free edges of the anterior and posterior mitral leaflets. Displacement in other areas of the leaflets (ie, near the commissures) may also play a role in mitral malcoaptation. Additional studies in this model of chronic infarction using a denser leaflet marker array are currently underway.

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References
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