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SURGERY FOR ADULT CARDIOVASCULAR DISEASE

EARLY SYSTOLIC MITRAL LEAFLET “LOITERING” DURING ACUTE ISCHEMIC MITRAL REGURGITATION

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Background: The mechanism by which incomplete mitral leaflet coaptation develops during ischemic mitral regurgitation is debated, with recent studies suggesting that incomplete mitral leaflet coaptation may be due to apically displaced papillary muscle tips. Yet quantitative in vivo three-dimensional mitral leaflet motion during ischemic mitral regurgitation has never been described. **Methods:** Radiopaque markers (sutured around the mitral annulus, to the central free mitral leaflet edges, and to both papillary muscle tips and bases) were imaged with the use of biplane videofluoroscopy in six closed-chest, sedated sheep before (control) and during induction of acute ischemic mitral regurgitation. Leaflet coaptation was defined as the minimum distance measured between edge markers during control conditions. **Results:** During control, leaflet coaptation occurred 23 ± 7 msec (mean $\pm$ standard error of the mean) after end-diastole, when left ventricular pressure was 27 ± 6 mm Hg. During ischemic mitral regurgitation, coaptation was delayed to 115 ± 19 msec after end-diastole ($p \leq 0.01$

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vs control [$n = 4$]) when left ventricular pressure was 88 ± 4 mm Hg. At end-diastole during ischemic mitral regurgitation, the mitral anulus area was $14\% \pm 2\%$ larger than control (7.4 ± 0.3 cm² vs 6.5 ± 0.2 cm², $p \leq 0.005$) as the result of the lengthening of muscular annular regions (76.0 ± 2.5 mm vs 70.5 ± 1.4 mm, $p \leq 0.01$). Mitral anulus shape (ratio of two diameters) at end-diastole was more circular during ischemic mitral regurgitation (0.79 ± 0.01 vs 0.71 ± 0.02 , $p < 0.01$). At end-diastole during ischemic mitral regurgitation, the posterior papillary muscle tip was displaced 1.5 ± 0.5 mm laterally and 2.0 ± 0.6 mm posteriorly ($p \leq 0.02$ vs control), but there was no apical displacement of either papillary muscle tip. **Conclusions:** Incomplete mitral leaflet coaptation during acute ischemic mitral regurgitation occurred early in systole, not at end-systole, and was due to "loitering" of the leaflets associated with posterior mitral anulus enlargement and circularization, as well as some posterolateral, but not apical, posterior papillary muscle tip displacement. These data suggest that early systolic mitral anulus dilatation and shape change and altered posterior papillary muscle motion are the primary mechanisms by which incomplete mitral leaflet coaptation occurs during acute ischemic mitral regurgitation. (*J Thorac Cardiovasc Surg* 1998;116:193-205)

Ischemic mitral regurgitation (MR) is a common clinical problem, developing after myocardial infarction in up to 19% of patients.¹ Some of these individuals experience progressive symptoms of congestive heart failure and ultimately require operative intervention to correct the MR. The choice of what type of operative repair to use has been generally based only on empirical notions gained from clinical experience, because the exact mechanism and pathogenesis of ischemic MR remain unknown. Traditionally, MR in patients with heart failure has been attributed to left ventricular (LV) dilatation.² Enlargement of the ventricle and LV regional systolic wall motion abnormalities, however, are associated with dynamic alterations in the three-dimensional (3-D) geometry of the mitral valve and subvalvular apparatus itself³; these secondary abnormalities are more likely to be the offending culprits responsible for ischemic MR.

Clearly, regurgitation occurs when there is incomplete mitral leaflet coaptation.⁴ Controversy arises, however, from the lack of comprehensive information regarding precisely what changes occur in the mitral valve apparatus during myocardial ischemia that cause incomplete mitral leaflet coaptation. Previous clinical and experimental reports have suggested a myriad of sometimes conflicting possibilities, including ischemic papillary muscle (PM) dysfunction,^{5,6} tethering of leaflets by apically displaced PM tips,^{7,8} leaflet prolapse secondary to PM

stretching,⁹ and dilatation and other geometric alterations in the mitral anulus (MA).¹⁰⁻¹² These proposed mechanisms do not fully explain the development of ischemic MR; for example, simple ring annuloplasty would not be expected to be effective in patients with ischemic MR if the responsible mechanism were merely related to restricted leaflet motion (Carpentier type III)¹³ or alterations in the 3-D geometry of PM tips.

It is important to note that none of these previous studies directly investigated the acute development of incomplete mitral leaflet coaptation by assessing in vivo 3-D mitral leaflet motion in a quantitative manner during ischemic MR. Additionally, these previous reports focused on end-systolic observations and largely ignored potential alterations in mitral valve geometry that may occur at end-diastole and in early systole, when normal mitral valve closure occurs. As such, previously suggested mechanisms cannot fully account for the development of ischemic MR because they did not include measurement of the timing and other abnormalities in leaflet coaptation.

In this study, using myocardial marker technology¹⁴ in an ovine preparation, we analyzed continuous 3-D motion of the mitral leaflet edges simultaneously with LV, PM, and MA dynamics in vivo to define more clearly the mechanical pathogenesis of incomplete mitral leaflet coaptation during acute ischemic MR.

Methods

Surgical preparation. Six healthy adult castrated male sheep (62 ± 10 kg [mean $\pm$ standard deviation]) were prepared for surgery,¹⁵ and miniature tantalum radiopaque helices were inserted into the LV wall and septum, as described previously.¹⁶

On cardiopulmonary bypass with the heart arrested, miniature gold radiopaque markers were sutured to the tips and bases of both PMs and to the central edges (ventricular surface) of both mitral leaflets, as shown in Fig. 1. Additional markers were sutured to the central midbellies and bases (near the MA) of both leaflets (three on the anterior and one on the posterior), but these markers were not analyzed in the current study. Eight additional miniature tantalum radiopaque markers were sutured equidistantly around the circumference of the MA, one near each commissural area (markers 1 and 5) and three along the perimeters of the anterior (markers 6 through 8) and posterior (markers 2 through 4) leaflets. A micromanometer pressure transducer (P4.5-X6; Konigsberg Instruments, Inc., Pasadena, Calif.) was placed in the LV chamber via the apex.

Experimental protocol. After 8 ± 2 (mean $\pm$ SD) days, each animal was taken to the experimental animal cardiac catheterization laboratory for hemodynamic and videofluorographic data acquisition. Details of the techniques used have been previously reported.¹⁵ UL-FS49 (Boehringer-Ingelheim, Ridgefield, Conn.), a highly specific negative chronotropic agent that does not change the QT interval, inotropic state, or systolic or diastolic blood pressure,¹⁷ was administered (8 mg intravenously) to reduce the heart rate (facilitating subsequent cinefluoroscopic visualization and tracking of marker motion). To minimize reflex sympathetic and parasympathetic responses that occur in conscious animals, autonomic blockade was accomplished with a low-dose intravenous infusion of esmolol (20 to 50 μ g/kg/min, titrated to reduce heart rate below 110 min^{-1}), and atropine sulfate (0.01 mg/kg intravenously).

An 8F coronary guiding catheter (Powerguide; Advanced Cardiovascular Systems, Inc., Temecula, Calif.) was advanced into the left main coronary artery over a 0.014 inch floppy guide wire (HI-TORQUE; Advanced Cardiovascular Systems, Inc.) through the 8F left femoral artery sheath. A conventional 3.0 mm nonperfusion balloon dilation catheter was then advanced through the guiding catheter into the mid-left circumflex coronary artery (distal to the first obtuse marginal artery).

For all data acquisition runs, hearts were in normal sinus rhythm, and ventilation was arrested briefly at end-expiration. All hemodynamic and biplane videofluoroscopic data recordings were obtained during steady-state conditions and over a physiologic range of peak LV systolic pressures during vena caval occlusion. Data recordings were obtained first immediately before induction of ischemia (control data). After 3 to 5 minutes of stabilization, the balloon dilatation catheter in the mid-left circumflex artery was inflated to 8 atmospheres completely occluding the artery. The balloon was kept inflated for 3.1 ± 0.3 (mean $\pm$ SD) minutes, producing acute posterolateral LV wall ischemia, resulting in MR as verified and graded (by a single observer [A.F.B.] as none,

Fig. 1. Schematic representation of the marker array. The nine subepicardial LV markers, four PM markers, and two mitral leaflet markers are depicted as *black dots*. The eight MA markers are depicted as *numbered circles*. APM, Anterior papillary muscles; PPM, posterior papillary muscles.

mild to moderate, or moderate to severe) using transthoracic Doppler echocardiography; data recordings were repeated during coronary artery balloon occlusion (ischemic MR data). Data from premature ventricular contractions and immediate after extrasystolic beats were discarded.

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 (DHEW [NIH] Publication 85-23, revised 1985). This study was approved by the Stanford Medical Center Laboratory Research Animal Review Committee and conducted according to Stanford University policy.

Data acquisition. Images were acquired with the animal in the right lateral decubitus position with a Philips Optimus 2000 biplane Lateral ARC 2/Poly DIAGNOST C2 system (Philips Medical Systems, North America Company, Pleasanton, Calif.) with the image intensifiers in 9° fluoroscopic mode. Data from the two radiographic views were digitized and processed to yield 3-D coordinates of each marker every 16.7 msec. Specific details of this data acquisition procedure have been described previously.¹⁶

Data analysis. Data from two consecutive steady-state beats during both control and acute ischemic MR conditions were averaged and defined as "control" and "ischemic" data, respectively.

Hemodynamics. For each cardiac cycle, the time of end-diastole was defined as the videofluoroscopic frame containing the beginning of positive deflection in electrocardiographic voltage (R-wave), and end-systole was defined as the videofluoroscopic frame immediately before

Fig. 2. Diagram demonstrating Θ_{AML} and Θ_{PML} , as calculated in degrees from the reference chord between MA markers 3 and 7. Mitral leaflet edge markers are represented by *black dots*.

the frame that contained the point of peak negative LV rate of pressure rise (dP/dt).

LV volume. Instantaneous LV volume was calculated with a multiple elliptic cylindric/cone model.¹⁸ The eight LV epicardial markers, eight MA markers, and one apical marker (Fig. 1) define three cross-sectional marker layers from base to apex. LV volume was computed as the sum of the volumes of two elliptic cylinders and one elliptic cone, as previously described.¹⁶ Although this computed volume included myocardial volume, we have previously shown that changes in this calculated volume accurately reflect changes in LV chamber volume.¹⁹ Because the LV volume calculations were made from epicardial measurements, the calculated ejection fractions are underestimates of the true ejection fractions.

Systolic LV function. We determined LV end-systolic pressure (P_{es}) and volume (V_{es}) during preload reduction using an iterative computer algorithm to define the end-systolic pressure/volume relationship to assess LV systolic performance.²⁰ Least-squares linear regression was used to fit a line of the form:

$$P_{es} = E_{es}(V_{es} - V_0)$$

to these end-systolic points, where E_{es} and V_0 are the slope and volume axis intercept of the end-systolic pressure/volume relationship, respectively.

Mitral leaflet dynamics. Mitral leaflet coaptation was defined as the minimum distance (5 mm) measured in 3-D space between the leaflet edge markers during control conditions. None of the animals had MR by transthoracic Doppler echocardiography at this time. Leaflet edge position in 3-D space was further defined by calculating the angle (degrees; Fig. 2) between an MA reference chord (defined from MA marker 3 to 7) and vectors from MA marker 7 to the anterior leaflet edge marker (AML), and from MA marker 3 to the posterior leaflet edge marker (PML).

MA and PM geometry. MA area and perimeters were computed from 3-D marker coordinates, without assuming circular or planar geometry. MA area was calculated as the sum of six triangular areas derived from triplets of MA marker coordinates, and partial MA perimeters were calculated as the sums of contiguous MA segment lengths (Fig. 1). MA and PM dimensions were also computed from 3-D marker coordinates. The septal-lateral MA dimension was calculated as the linear distance in 3-D

space between MA markers 3 and 7 (middle of the anterior MA to a corresponding locus on the posterior MA), and the commissure-commissure MA dimension was computed as the linear distance in 3-D space between MA markers 1 and 5 (Fig. 1). The septal-lateral/commissure-commissure ratio was used as a measure of MA eccentricity (a ratio of 1.0 signifies a circle, with eccentricity increasing as the ratio decreases). PM lengths were calculated as linear distances in 3-D space between the PM tip and base markers.

Mitral apparatus shape was analyzed further with a 3-D coordinate system defined with the origin at the midpoint of the commissural markers (markers 1 and 5), and the negative z-axis directed through the LV apical marker (i.e., along the LV long axis). This system allowed the description of the location of any marker in 3-D coordinates; positive z coordinates were nearer the atrium, and negative z coordinates were closer to the LV apex.

Statistical analysis. All data are reported as mean $\pm$ 1 standard error of the mean, unless otherwise stated. Hemodynamic and marker-derived data from two consecutive steady-state beats in six hearts were time-aligned at the upstroke of the electrocardiographic R-wave (end-diastole; only four animals contributed data to the leaflet edge marker analysis because at least one leaflet marker had become dislodged postoperatively in the other two sheep). The mean and SEM for each variable were computed for the 12 beats (8 beats for leaflet data) at end-diastole and at 16 time samples before (267 msec) and after end-diastole, such that a curve could be generated depicting the behavior of any variable throughout one cardiac cycle (534 msec in this experiment [104 min⁻¹]). Repeated measures of analysis of variance was used to detect whether there appeared to be significant differences between end-diastole and end-systole values of the variables of interest and whether these values were affected by the factor of circumflex coronary artery balloon occlusion (i.e., ischemia). In cases where a difference was evident, mean differences were tested for significance (compared with zero) by Student's *t* test for dependent observations, with Bonferroni's correction for multiple comparisons.

Results

Postmortem examination of excised hearts revealed all LV epicardial markers to be within 1 mm of the epicardial surface, all eight MA markers to be within 1 mm of the MA (as defined by the leaflet-left atrial endocardium junction), and all the PM markers to be present.

Hemodynamics. Acute MR was successfully induced in all six sheep by circumflex coronary artery balloon occlusion; four sheep had mild to moderate MR, and two had moderate to severe MR. The two sheep that were missing leaflet edge markers at the time of data acquisition were in the mild to moderate MR group. No animal had evidence of MR before circumflex occlusion.

The average heart rate for all sheep did not differ between preischemic control and acute ischemic MR conditions (107 ± 5 vs 101 ± 8 min⁻¹, $p = \text{NS}$). End-diastolic LV pressure did not increase with acute ischemia (16 ± 2 vs 14 ± 1 mm Hg, $p = \text{NS}$), but peak systolic LV pressure fell significantly 141 ± 8 vs 102 ± 6 mm Hg, $p \leq 0.005$). Additionally, although global LV systolic function, as assessed by E_{es} , did not change significantly during ischemia (3.0 ± 0.3 mm Hg/ml vs 3.3 ± 0.09 mm Hg/ml, $p = \text{NS}$), LV ejection fraction decreased by $30\% \pm 8\%$ ($21\% \pm 1\%$ vs $14\% \pm 1\%$, $p \leq 0.02$); LV stroke work decreased by $47\% \pm 19\%$ (4024 ± 561 mm Hg · ml vs 2030 ± 367 mm Hg · ml, $p \leq 0.005$), and LV dP/dt_{max} decreased by $22\% \pm 5\%$ (1622 ± 103 mm Hg/sec vs 1254 ± 90 mm Hg/sec, $p \leq 0.001$). These hemodynamic alterations are consistent with a moderate degree of acute regional LV ischemia accompanying balloon occlusion.

Mitral leaflet dynamics. Fig. 3 shows the changes in LV pressure and distance between the mitral leaflet edge markers versus time for all animals during both control and ischemic conditions. During control, mitral leaflet edge marker separation reached 5 mm (defined as *coaptation*) 23 ± 7 msec after end-diastole, when LV pressure was 27 ± 6 mm Hg ($19\% \pm 4\%$ of peak systolic LV pressure). During acute ischemic MR, mitral leaflet edge marker separation also ultimately reached 5 mm, but the time of this coaptation was significantly delayed to 115 ± 19 msec after end-diastole ($p \leq 0.01$ vs control), when LV pressure had already risen to 88 ± 4 mm Hg ($86\% \pm 3\%$ of peak systolic LV pressure). It is important to note that abnormalities in the motion of both leaflets contributed to this delayed coaptation (Fig. 2). At end-diastole with acute ischemia, Θ_{AML} increased from 36 ± 1 degrees to 41 ± 2 degrees ($p \leq 0.001$), and Θ_{PML} increased from 61 ± 1 degrees to 65 ± 3 degrees ($p \leq 0.01$); however, at end-systole there were no such differences between control and ischemic conditions in Θ_{AML} and Θ_{PML} . Moreover, there was no apical displacement of either mitral leaflet edge marker at the time of coaptation. The distance from the MA (measured along the LV long axis) to the point of coaptation did not change during acute ischemia (7.5 ± 0.5 mm vs control 8.0 ± 0.4 mm, $p = \text{NS}$), even though the timing of coaptation differed between the two conditions.

MA shape, geometry, and motion. Fig. 4 shows the changes in MA area, partial MA perimeters (muscular and fibrous regions), septal-lateral and

commissure-commissure dimensions, and septal-lateral/commissure-commissure ratio versus time for all animals during control and acute ischemic MR conditions. The area of the MA orifice was larger during acute ischemic MR than during control at all times in the cardiac cycle. Although overall MA area shrinkage from maximum to minimum was reduced during acute ischemia ($11\% \pm 1\%$ vs $15\% \pm 2\%$, $p \leq 0.02$), the amount of presystolic area shrinkage was unchanged ($74\% \pm 16\%$ vs $85\% \pm 6\%$ of total area shrinkage, $p = \text{NS}$). More important, however, the increase in MA area during acute ischemia reached a maximum of $14\% \pm 2\%$ larger than control at end-diastole (7.4 ± 0.3 cm² vs 6.5 ± 0.2 cm², $p \leq 0.005$) but was only $9\% \pm 2\%$ larger than control at end-systole (7.4 ± 0.3 cm² vs 6.8 ± 0.2 cm²). This MA enlargement involved dilatation of the muscular regions of the MA only (e.g., 76.0 ± 2.5 mm vs 70.5 ± 1.4 mm at end-diastole, $p \leq 0.01$); the length of the intertrigonal (or anterior) MA region was unchanged during acute ischemia at all times in the cardiac cycle, as depicted graphically in Fig. 5.

The MA septal-lateral and commissure-commissure dimensions reflected changes in MA shape. As seen in Fig. 4, septal-lateral MA dimension was larger during acute ischemia than during control conditions throughout the cardiac cycle, with a maximum difference of $13\% \pm 3\%$ again occurring at end-diastole (27.8 ± 0.6 mm vs 24.6 ± 0.2 mm, $p \leq 0.005$). The commissure-commissure dimension increased slightly with acute ischemia but was significantly larger than control only at end-systole (34.6 ± 0.6 mm vs 33.6 ± 0.5 mm, $p \leq 0.02$), when the leaflets had already coapted; at end-diastole this difference was not significant (35.3 ± 0.9 mm vs 34.6 ± 0.6 mm, $p = \text{NS}$). Consequently, the annular septal-lateral/commissure-commissure ratio was significantly larger during acute ischemia (i.e., a more circular anulus) throughout the cardiac cycle, again with the greatest relative difference between control and ischemic conditions occurring at end-diastole (0.79 ± 0.01 vs 0.71 ± 0.02 , $p \leq 0.01$). Additionally, at end-systole during acute ischemia there was reduction in the height above the intercommissural midpoint of the anterior MA “saddlehorn” near the aortic valve (6.1 ± 0.8 mm vs 7.7 ± 0.9 mm) as previously reported,¹² but this shape perturbation was not observed at end-diastole.

LV and PM dynamics and geometry. To determine whether the observed end-diastole MA enlargement was simply a consequence of LV dilata-

Fig. 3. LV pressure (LVP; solid and open squares) and mitral leaflet edge separation (solid and open circles) versus time for control (solid line) and ischemic MR (dashed line) conditions. Data are composite average values for all animals ($n = 4$ for leaflet edge separation), with error bars representing ± 1 SEM. The graph depicts one cardiac cycle extending from beginning diastole to end-systole (vertical shaded box), with data aligned at the upstroke of the electrocardiographic R wave (end-diastole, defined by the vertical line at $t = 0$). Delayed mitral leaflet coaptation during ischemic MR occurred in early systole, when the leaflets “loitered” (arrow) before ultimately coapting in mid-systole. Note that the valve was closed at end-systole during ischemic MR.

tion, we compared various LV dimensions before and during acute ischemia. Fig. 6 depicts LV volume, the distances between the anterior and posterior PM tips and bases, and the lengths of both PMs versus time. Although LV volume was larger at end-systole during acute ischemia (134 ± 18 ml vs 122 ± 14 ml, $p \leq 0.001$), LV volume at end-diastole was not changed (157 ± 21 ml vs 154 ± 21 ml, $p = \text{NS}$). Similarly, the PM tip-to-tip (26.6 ± 0.6 mm vs 26.3 ± 0.6 mm, $p = \text{NS}$) and PM base-to-base (25.9 ± 2.1 mm vs 25.6 ± 1.8 mm, $p = \text{NS}$) dimensions at end-diastole did not change during acute ischemia. Finally, the end-diastolic length of the LV long axis was not changed by acute ischemia (81.8 ± 2.7 mm vs 82.1 ± 2.9 mm, $p = \text{NS}$). Not surprisingly, because ejection fraction was significantly reduced, LV volume at end-systole was increased during acute ischemia (135 ± 7 ml vs 123 ± 6 ml, $p \leq 0.001$), with corresponding increases at end-systole in the PM tip-to-tip (23.1 ± 0.7 mm vs 20.1 ± 0.7 mm, $p \leq 0.01$) and PM base-to-base (20.4 ± 1.9 mm vs 17.6 ± 1.1 mm, $p \leq 0.05$) dimensions. These increases in LV dimensions at end-systole during acute ischemia, however, could not have contributed to the observed incomplete mitral leaflet coaptation, because the valve was already closed at this end-systolic time.

Analysis of PM dynamics (Fig. 6) revealed that anterior PM systolic shortening (from end-diastole to end-systole) was unaffected by acute posterolateral ischemia, as expected. Shortening of the posterior PM was abolished by acute ischemia, and the posterior PM actually lengthened during systole ($-3\% \pm 3\%$ vs $9\% \pm 1\%$, $p \leq 0.02$); this lengthening resulted in increased posterior PM length at end-systole (22.1 ± 2.2 mm vs 19.6 ± 1.8 mm, $p \leq 0.02$). On the other hand, posterior PM length was unchanged during acute ischemia at end-diastole (21.5 ± 2.1 mm vs 21.8 ± 2.2 mm, $p = \text{NS}$), the time when leaflet “loitering” began. We also compared the position in 3-D space of both PM tips before and during acute ischemia to determine whether either PM was abnormally displaced at the time of incomplete mitral leaflet coaptation. As shown in Figs. 5 and 7, the position of the anterior PM tip did not change at end-diastole during acute ischemia, but the posterior PM tip became dislocated 1.5 ± 0.5 mm towards the LV lateral wall and 2.0 ± 0.6 mm towards the posteromedial commissural area ($p \leq 0.02$ vs control). It is important to note that this displacement allowed the position of the posterior PM tip to remain relatively constant with relation to the MA (i.e., the posterior PM was displaced in a similar direction as MA enlargement; Fig. 5). Al-

Fig. 4. MA area, length of muscular regions of the MA (*Musc.*), length of the intertrigonal fibrous regions of the MA (*Fibr.*), septal-lateral dimension (*SL*), commissure-commissure dimension (*CC*), and ratio of septal-lateral to commissure-commissure dimensions (*SL/CC*) versus time for control (solid line) and ischemic MR (dashed line) conditions. Data are composite average values for all animals, with error bars representing 1 SEM. The graphs each depict one cardiac cycle extending from beginning diastole to end-systole (vertical shaded box), with data aligned at the upstroke of the electrocardiographic R wave (end-diastole, defined by the vertical line at $t = 0$).

though at end-systole, there was some displacement of the posterior PM tip toward the MA (0.9 ± 0.3 mm) and of the anterior PM tip toward the LV apex (0.6 ± 0.2 mm), we observed no such displacement of either PM tip at the time of incomplete mitral leaflet coaptation (Fig. 7).

Discussion

Various mechanisms have been proposed to explain the development of MR after myocardial ischemia or infarction. Most of these theories fo-

Fig. 5. Projection of the MA, eight annular markers (numbered), and two PM tip markers in the zero plane, as viewed from the left atrium at end-diastole for control (solid line and circles) and ischemic MR (dashed line, open circles) conditions. Data are group mean marker position, with the origin at the intercommissural midpoint (between markers 1 and 5). Note that the annular enlargement during ischemic MR was confined to the muscular regions of the annulus (i.e., all segments but those between markers 6, 7, and 8) and that the PPM tip was displaced in a similar direction as annular enlargement. *RFT*, Right fibrous trigones; *PC*, posteromedial commissural areas; *PPM*, posterior papillary muscles; *LFT*, left fibrous trigones; *APM*, anterior papillary muscles; *AC*, anterolateral commissural areas.

cused on geometric alterations occurring within the ventricle and/or mitral subvalvular apparatus during acute myocardial ischemia. It has previously been thought that the time within the cardiac cycle when these acute changes are most important is late systole and end-systole, and thus any observed end-systolic changes in mitral apparatus geometry were promoted as causative factors in the pathogenesis of ischemic MR. In this first study of 3-D mitral leaflet geometry and motion, we present direct novel evidence of incomplete mitral leaflet coaptation occurring *in vivo* in early systole during acute posterolateral LV wall ischemia, coinciding with significant end-diastolic geometric alterations in the mitral valve complex.

Mitral leaflet dynamics. We defined central leaflet coaptation as the minimum distance (5 mm) measured between the leaflet edge markers during control conditions, when no MR was noted on Doppler echocardiography. As such, it can be seen from Fig. 3 that the mitral valve was ultimately

Fig. 6. LV volume (*LVV*), distance between papillary tips (*Tip-Tip*), distance between papillary bases (*Base-Base*), length of anterior PM (*APM*), and length of posterior PM (*PPM*) versus time for control (*solid line*) and ischemic MR (*dashed line*) conditions. Data are composite average values for all animals, with error bars representing ± 1 SEM. The graphs each depict one cardiac cycle extending from beginning diastole to end-systole (*vertical shaded box*), with data aligned at the upstroke of the electrocardiographic R wave (end-diastole, defined by the *vertical line* at $t = 0$). Note that LV enlargement and posterior PM lengthening occurred at end-systole only, when the valve was already closed.

closed by the time of end-systole during both control and acute ischemic MR conditions; the delay in leaflet coaptation during acute ischemic MR occurred in early systole only. Importantly, this delayed closure involved abnormal motion of both mitral leaflets, indicating that proper closing of both mitral leaflets is essential for effective valve closure.

Also, the locations (with relation to the MA) of both central leaflet edge markers at the time of coaptation were unchanged by acute ischemia, that is, there was no "apical displacement" of the coaptation zone as suggested previously.^{7,8} These earlier studies, however, were based on two-dimensional echocardiographic data acquisition and therefore

could not accurately determine the point of coaptation in 3-D space. The current 3-D marker data therefore shed new light on the pathogenesis of acute ischemic MR.

MA shape, geometry, and motion. As compared with control measurements, MA area was larger during acute ischemic MR throughout the entire cardiac cycle, with the greatest relative increase being observed at end-diastole, precisely the time when delayed leaflet coaptation began. This enlargement was confined to the muscular, mostly posterior, MA (Figs. 4 and 5).^{12, 21} It may seem as though a $14\% \pm 2\%$ increase in MA area would be insufficient to produce incomplete mitral leaflet coaptation given the tremendous natural redundancy or “surplus” of leaflet tissue available, but this value is nearly equivalent to the overall maximum to minimum area shrinkage of $15\% \pm 2\%$ that occurs in the normal ovine MA. More important, during acute ischemia, the smallest MA area at any time in the cardiac cycle ($7.5 \pm 0.3 \text{ cm}^2$) was equivalent to the largest MA area reached during control conditions ($7.5 \pm 0.2 \text{ cm}^2$), emphasizing the physiologic significance of this degree of MA enlargement. Although Gorman and associates²² have suggested that acute ischemic MR does not result from MA dilatation, their data pertained to end-systole measurements only; they did not discuss end-diastolic measurements. Interestingly, the finding reported by Gorman and associates²² of flattening of the MA “saddlehorn” at end-systole concurs with our observations at end-systole; however, no such flattening occurred at end-diastole, when the period of leaflet “loitering” started. Thus this perturbation in annular height cannot explain our new findings of early systolic incomplete mitral leaflet coaptation.

The MA orifice was not only dilated during acute ischemic MR, but its cross-sectional shape was altered as well. Because the septal-lateral dimension enlarged significantly more than the commissure-commissure dimension during acute ischemia at end-diastole, the MA was more circular in early systole when incomplete mitral leaflet coaptation occurred. This increase in septal-lateral dimension and subsequent annular “circularization” in conjunction with MA dilatation would tend to compound the separation of the leaflet edge markers, thereby augmenting the extent of incomplete mitral leaflet coaptation.

We previously demonstrated similar changes in MA orifice size and shape at end-diastole when normal left atrial contraction was abolished,¹⁵ but in

Fig. 7. Schematic of the MA with eight annular markers (numbered), anterior PM (APM) with tip and base markers, and posterior PM (PPM) with tip and base markers in the anterior-posterior projection at end-diastole for control (solid line and circles) and ischemic MR conditions (dashed line, open circles). Data are mean marker positions, with the origin at the intercommissural midpoint (between annular markers 1 and 5). Negative values along the ordinate are toward the LV apex. Note that neither PM tip was displaced apically at end-diastole (the time when leaflet loitering began). AC, Anterolateral commissural areas; PC, posteromedial commissural areas.

the current study there was no evidence of less presystolic MA area shrinkage during acute ischemia ($74\% \pm 16\%$ vs $85\% \pm 6\%$, $p = \text{NS}$), probably reflecting no change in normal left atrial function. Because both atrial and ventricular fibers insert into the mitral ring^{23, 24} and because the fibers of ventricular origin are circumferentially arranged (although those of atrial origin are perpendicularly oriented),²⁵ it is likely that the observed MA geometry changes resulted from diminished contractile function and dyskinesia of the LV fibers inserted into the posterior mitral ring. Such dyskinesia and loss of contractile function would result in lengthening of these fibers at all times in the cardiac cycle. As such, overall MA orifice size was larger and its shape was more circular, even though presystolic area shrinkage was conserved.

LV and PM dynamics and geometry. These observations indicate that LV dilatation or shape change cannot be implicated as causing acute ischemic MR. Although these data agree with previously reported findings that myocardial ischemia produces LV enlargement and probable LV shape changes at end-systole,^{20, 26} there were no such changes at end-diastole, when the observed delay in mitral

leaflet coaptation started. As such, these LV geometric changes cannot explain early systolic MR during acute myocardial ischemia. The same is true of alterations in PM geometry. Although the posterior PM was dyskinetic during systole, resulting in end-systolic lengthening (as previously reported^{6,9}), there was no difference in length of either PM during the time of incomplete mitral leaflet coaptation in early systole. Thus prolapse of leaflet edges attached to an elongated posterior PM cannot explain early systolic incomplete mitral leaflet coaptation. Additionally, we found no evidence of apical displacement of either PM tip in early systole at the time of incomplete mitral leaflet coaptation. This finding concurs with previous observations from this laboratory in dogs where apical displacement of either PM tip was absent in early systole during acute ischemic MR.²⁷ We did, however, detect other small displacements in the 3-D end-diastolic location of the posterior, but not the anterior, PM tip during ischemia, that is, the posterior PM tip moved laterally and posteriorly. The location of the posterior PM tip in relation to the MA, however, was not significantly different, as seen in Figs. 5 and 7. Consequently, it is likely that mechanisms other than PM dysfunction and PM apical displacement are responsible for the development of acute ischemic MR in sheep.

Surgical implications. The observations in this experiment reveal that acute posterolateral LV ischemia results in early systolic incomplete mitral leaflet coaptation and MR, which is associated primarily with significant end-diastolic MA enlargement and shape change, and small alterations in posterior PM tip location. Conversely, no changes in LV geometry, leaflet prolapse, or apical displacement of any part of the mitral apparatus were seen at end-diastole when leaflet "loitering" started. Thus these data do not support the clinical notion that acute ischemic MR is merely an end-systolic phenomenon. It is true that multiple 3-D geometric perturbations in the mitral subvalvular apparatus do occur at end-systole, as this and previous experiments^{6,8,9,21,22,26} have demonstrated; however, it is possible that most of the MR actually occurs earlier solely as the result of early systolic incomplete mitral leaflet coaptation in the central regions of the leaflets, which is attributable primarily to MA dilatation. This early systolic MR during acute ischemia may thus be the initial inciting event that ultimately leads to more MR and then chronic LV volume overload, with eventual subsequent

worsening of MR over time. As such, these data may provide a new foundation for use of ring annuloplasty (i.e., beneficial effects at end-diastole and during early systole). It also is clear why a ring can work in patients with ischemic MR. By reducing the size of the MA, the leaflet edges are brought closer together thereby allowing coaptation to occur more readily. Because MA dilatation was confined to the muscular (posterior) MA, patients with ischemic MR may only need a partial (posterior) annuloplasty ring rather than a complete ring; conversely, a complete ring with restoring "hoop" forces applied across the septal-lateral axis may minimize the end-diastolic "circularization" we observed. Moreover, detection of incomplete mitral leaflet coaptation at the center of the mitral valve leaflets during ischemic MR lends support to the "edge-to-edge" or "bow tie" technique of mitral valve repair proposed by Fucci and colleagues.²⁸ Suturing the central free edges of the mitral leaflets together will certainly inhibit the development of central incomplete mitral leaflet coaptation even in the absence of an annuloplasty ring; however, incomplete mitral leaflet coaptation could theoretically still occur on either side of the suture involving the "figure of 8" double mitral orifice.

On the other hand, it is important to consider the possibility that the observed end-systolic 3-D geometric perturbations in the mitral subvalvular apparatus also caused MR; in other words, acute ischemic MR (at least in sheep) could also be due to incomplete mitral leaflet coaptation in the medial and lateral regions of the valve leaflets, which were not examined in this experiment. Future 3-D dynamic studies of leaflet motion in these other valve regions are necessary to define more completely the behavior of all parts of the mitral leaflets throughout the entire cardiac cycle. In addition, further studies of MA fixation with and without myocardial ischemia are needed to determine whether or not MA area reduction alone (i.e., isolated ring annuloplasty) is sufficient to prevent the development of ischemic MR. Ongoing sheep studies in our laboratory have been designed to address these questions.

Limitations. The use of myocardial markers for 3-D assessment of cardiac dynamics has obvious limitations. First, although this technology allows accurate and reproducible determination of 3-D marker position every 16.7 msec with a mean overall error of only 0.1 ± 0.6 mm,²⁹ it requires suturing small metallic markers to the area of interest, in this case the mitral leaflets, MA, and PM tips and bases.

The possibility of markers interfering with normal motion of these structures, particularly the leaflets, should be considered; however, because the markers are small (20 ± 6 mg) their effect is probably inconsequential. In fact, preliminary data from our laboratory revealed that the peak velocity of the anterior mitral leaflet edge marker (calculated from 60 Hz marker data) was 0.49 ± 0.03 m/sec, which is of the same order of magnitude as the 0.3 to 0.4 m/sec speed of the anterior mitral leaflet in human beings and in sheep without leaflet markers (calculated from M-mode echocardiography recorded at 225 Hz).

Second, because markers were inserted only on the central region of the mitral leaflets in this initial study of 3-D mitral leaflet motion, no data are available concerning coaptation or motion of other parts of the leaflet edges. Thus in the present study we cannot rule out the possibility that incomplete mitral leaflet coaptation occurred posteromedially or anterolaterally. This investigation, however, clearly demonstrates that incomplete mitral leaflet coaptation during acute ischemic MR occurs at least in the central portion of the valve and that this phenomenon takes place in early systole. Although adding more markers to other aspects of the mitral valve leaflets would increase our knowledge about the mechanism(s) of ischemic MR in other regions of the leaflets, the additional marker mass might be sufficient to exert inertial effects that could artifactually perturb leaflet motion independent of ischemia. We are currently working to design an animal model with smaller markers arranged in a denser array on the leaflet edges to elucidate more clearly the behavior of the anterolateral and posteromedial aspects of the mitral valve during ischemic MR.

Other limitations lie in the use of the animal model. This experiment was conducted in mature sheep, which have been reported to have a less well-defined posterior MA than human beings, with a greater amount of left atrial tissue above and below the mitral leaflet hinge points. A recent study has shown, however, that the amount of left atrial muscle fiber in the human mitral ring is quite variable; therefore it may be more like the sheep's MA than previously thought.²⁴ In addition, this study examined only the effects of acute posterolateral LV wall ischemia. Other ischemic insults, for example regional anterior wall or global LV ischemia, both acute and chronic, need to be investigated. Because chronic volume overload as the result of MR will ultimately result in LV remodeling

and other geometric alterations in the ventricle and mitral subvalvular apparatus, the inferences drawn from acute studies may not be directly applicable to dilated human hearts with limited LV systolic reserve as a result of chronic MR because of previous myocardial ischemia and/or infarction. Additional experiments in an animal model of long-standing LV volume overload as a consequence of chronic MR are necessary to define the relevance of these data to the broad spectrum of current surgical practice. We are currently considering an experimental model of dilated cardiomyopathy to address this question.

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Discussion

Dr. Steven F. Bolling (*Ann Arbor, Mich.*). As someone who also uses this model on our laboratory, I know how hard this information is to gather. We also have the feeling in this ischemic syndrome that loitering (although we did not use that word before today, but we will in the future) was what the mitral leaflets were doing; they were slow to get the idea of where they were supposed to go. I have a number of questions for the authors. First, you describe different degrees of MR occurring in the sheep, ranging from mild in some to severe. Do you think there are different mechanisms in mild versus severe MR in these sheep or differing degrees of mechanisms for ischemic MR?

Second, the sheep anulus is anatomically not the same as the human anulus. Are there differences that can be seen in the human anulus?

Third, clinically most of us see chronic ischemic or chronic MR associated with ischemia, not acute ischemia, as this type of syndrome is described. What are the clinical implications of this in terms of chronic ischemia that has been ongoing for years and years?

Finally, in terms of clinical implications; all of these concepts result in an increase in MA size perhaps and a decrease in zone of coaptation. We agree that apical displacement of the PMs and cords are not part of this syndrome. But in terms of repairing these valves, reconstructing these valves, is it not the bottom line to increase the zone of coaptation and whether this occurs chronically or whether it is important, if you increase the zone of coaptation would that not take care of this syndrome in itself?

Dr. Glasson. Thank you for your comments, Dr. Bolling. With regard to the degree of MR, the animals in this experiment were all subjected to variable amounts of ischemia, ranging between 2 and 7 minutes. We believe that our observations pertain to the initial deformations in the geometry of the mitral valve complex that occur at the beginning of acute ischemia. The first deformation, then, appears to be MA dilatation, with LV volume overload probably ensuing subsequently. As such, the traditional idea that MR begets more MR makes sense. The degree of MR that we measured in these sheep may have varied between animals based on the amount of ischemia that each animal experienced. Also, it was difficult to determine the exact amount of MR present because the quantification was based on echocardiographic analyses and because the images obtained transthoracically are not as accurate as what we can see and calculate with markers. However, with regard to leaflet behavior, all animals with leaflet edge markers behaved identically, that is, all animals showed leaflet loitering during acute ischemia, and all animals had MR on echocardiography during this ischemia. As such, I do not believe that there were different mechanisms at work in different animals.

As far as the anatomy of the anulus, there are actually many papers in the literature with conflicting data as to

what type of fibers insert into the annular ring and where these insertions occur. For example, one paper suggests that sheep have a more muscular posterior anulus than do human beings, but a recent study by Angelini and associates [see reference 24] showed that variability in left atrial and LV muscle fiber insertions is present in the anuli of human beings similarly as in dogs, sheep, and cows; they could not pinpoint any obvious differences. The results of these many anatomic studies may be conflicting because of the diversity in the number of different individuals studied in each case; that is, if one only looks at five human anuli, the results are going to be quite different than if one looks at 500 anuli.

With regard to clinical implications, yes, you are correct. This is a very acute study, and a long-term model with chronic volume overload would likely produce different results. As I have shown, these animals did not have any increases in volume or long or short axis length of the left ventricle during incomplete mitral leaflet coaptation at end-diastole. As such, we believe that these annular changes are acute and occur before the volume overload that may distort ventricular geometry in the subacute or chronic setting. Such subsequent distortion in ventricular geometry may then in turn lead to more MR by various different mechanisms, including LV dilatation and further annular enlargement.

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