

# Edge-to-Edge Mitral Valve Repair Without Ring Annuloplasty for Acute Ischemic Mitral Regurgitation

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**Background**—Alfieri edge-to-edge mitral repair has been used clinically with ring annuloplasty to correct ischemic mitral regurgitation (IMR), but its efficacy without concomitant ring annuloplasty has not been described in this setting.

**Methods**—Seventeen sheep underwent implantation of 9 radiopaque markers on the left ventricle, 8 on the mitral annulus (MA), 1 on each papillary muscle (PM) tip, and 1 on the anterior and posterior leaflet edges near the anterior and posterior commissures. Alfieri repair was performed in 7 animals, and 10 were controls. Biplane videofluoroscopy and transesophageal echocardiography (TEE) were performed (open chest) before and continuously during left circumflex coronary artery occlusion to induce acute IMR. MA area (MAA), anterior (APM), and posterior (PPM) papillary muscle tip distances to midseptal MA (“saddle horn”), and distance of each leaflet marker to the mitral annular plane were calculated from 3-dimensional marker coordinates at end-systole (ES).

**Results**—Severity of IMR was not different between groups ( $+1.9\pm 0.7$  versus  $+1.4\pm 0.5$  for Control and Alfieri, respectively;  $P$ =not significant [NS]). Mitral annular area (MAA;  $21\pm 15$  versus  $19\pm 9\%$ ;  $P$ =NS) and septal-lateral (SL) annular diameter ( $12\pm 6$  versus  $12\pm 11\%$ ;  $P$ =NS) increased similarly during ischemia. While PPM-saddle horn distance increased in both groups ( $1.5\pm 1.3$  and  $1.6\pm 1.4$  mm for Control and Alfieri, respectively;  $P<0.05$  versus preischemia), APM-saddle horn distance increased in Control ( $1.0\pm 1.2$  mm;  $P=0.03$ ) but not in the Alfieri animals ( $0.8\pm 0.8$  mm;  $P=0.07$ ). Leaflet edge displacements from the annular plane during ischemia were similar in both groups.

**Conclusions**—Alfieri repair did not prevent acute IMR nor alter ischemic valvular or subvalvular geometric perturbations. Adjunct surgical procedures, such as ring annuloplasty, are also necessary. (*Circulation*. 2003;108[suppl II]:II-122-II-127.)

**Key Words:** mitral valve repair ■ coronary artery disease ■ annuloplasty  
■ mitral regurgitation ■ ischemic mitral regurgitation

Surgical correction of IMR continues to be associated with suboptimal outcomes.<sup>1,2</sup> Currently, IMR is treated most often with ring annuloplasty.<sup>3</sup> As understanding of the pathophysiology of IMR has evolved, innovative mitral reparative surgical techniques, both at the annular and subvalvular level, have been proposed.<sup>4,5</sup> The Alfieri edge-to-edge mitral repair<sup>6</sup> has been used to treat various forms of mitral pathology,<sup>7-9</sup> including ischemic and functional mitral regurgitation.<sup>10,11</sup> This technique, usually with concomitant ring annuloplasty,<sup>12</sup> offers an expedient and simple method for certain forms of mitral pathology.<sup>9</sup> However, use of the edge-to-edge mitral repair in patients with IMR is very limited; thus, its efficacy in this challenging patient population remains unknown. Although some experimental data suggest that this technique may address the subvalvular perturbations associated with IMR,<sup>13</sup> many surgeons question whether there is any additional benefit derived

from leaflet approximation above that of ring annuloplasty. To evaluate the efficacy of the Alfieri mitral repair without ring annuloplasty in preventing acute IMR, sheep underwent simulated edge-to-edge mitral repair and subsequent acute posterolateral ischemia to induce acute IMR. The effect of leaflet approximation on annular and subvalvular geometry during acute ischemia was also examined.

## Methods

### *Surgical Preparation*

This experimental preparation has been described previously.<sup>14</sup> Seventeen adult male sheep had 8 subepicardial miniature tantalum helical markers inserted into the left ventricle along 4 equally spaced longitudinal meridians at 2 levels between left ventricular (LV) apex and base. Using cardiopulmonary bypass and cardioplegic arrest, 8 additional markers were sutured around the circumference of the MA, 1 marker was placed on the edge of each leaflet near the

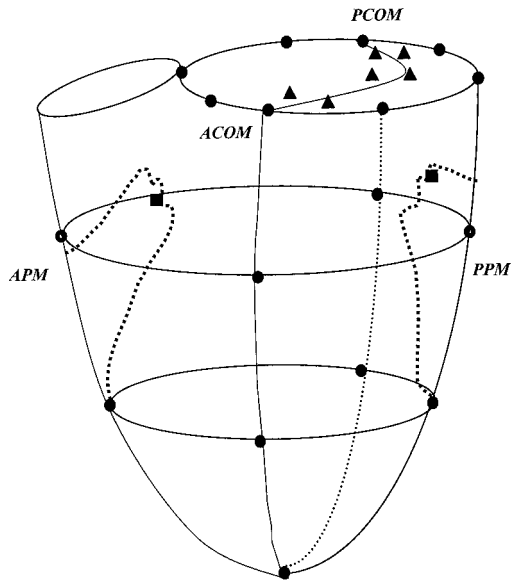
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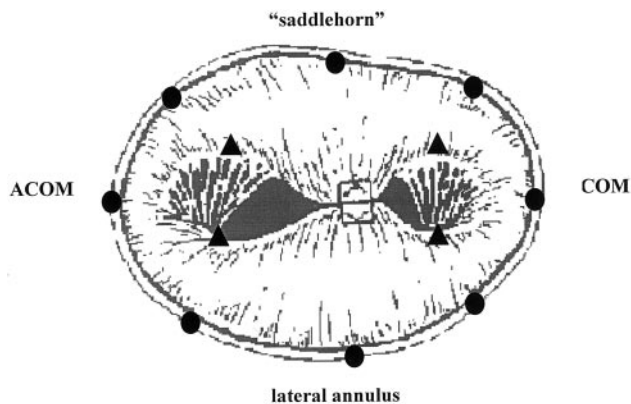
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**Figure 1.** Schematic illustration of the array of ventricular and annular (circles), PM tip (squares), and leaflet edge (triangles) markers used in the Control group. APM=anterior papillary muscle, PPM=posterior papillary muscle, ACOM=anterior commissure, PCOM=posterior commissure.

anterior and posterior commissures, and 1 marker was sutured on each PM tip (Figure 1). Ten animals had an additional marker placed on the central edge of each leaflet and underwent no additional surgery (Control group). In the other 7 animals, the centers of the anterior and posterior mitral leaflets were approximated with a 5-0 polypropylene suture (reinforced with 1 small Teflon-felt pledgets) placed  $\approx 5$  mm from each leaflet edge, which secured a miniature force transducer, as described previously,<sup>15</sup> serving as another radiopaque marker. The complete mitral annular and leaflet marker array for the Alfieri group is shown in Figure 2.

After completion of marker implantation, a silastic loop was placed around the proximal left circumflex coronary artery for creation of posterolateral LV ischemia. A micromanometer pressure transducer (PA4.5-X6; Konigsberg Instruments, Inc.) was placed in the LV chamber through the apex, and a second pressure transducer was advanced to the ascending aorta through a left carotid sheath.



**Figure 2.** Schematic representation of Alfieri edge-to-edge repair with central leaflet edge approximation resulting in a double-orifice valve. In this experiment, the leaflets were attached using a miniature force transducer. Annular (circles) and leaflet (triangles) markers are shown schematically. ACOM=anterior commissure, PCOM=posterior commissure, saddle horn=center of septal annulus. Modified from Fucci et al *Eur J Cardiothorac Surg.* 1995;9:621–626.

The animal was weaned from cardiopulmonary bypass, transferred immediately to the experimental animal catheterization laboratory, and then studied intubated, anesthetized (ketamine [1 to 4 mg/kg/h IV infusion] and diazepam [5 mg IV bolus as needed]) under open chest conditions. IV esmolol infusion (20–50  $\mu\text{g}/\text{kg}/\text{min}$ ) minimized reflex sympathetic responses. Simultaneous biplane videofluoroscopy, hemodynamic data recordings, and transesophageal color Doppler echocardiography (TEE) were carried out immediately before and continuously during proximal left circumflex occlusion [proximal to first obtuse marginal (OM) branch]. Mitral regurgitation (MR) was graded subjectively by an experienced echocardiographer (DL) 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).

All of the 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 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

Images were acquired with the animal in the right lateral decubitus position using a Philips Optimus 2000 biplane Lateral ARC 2/Poly DIAGNOST C2 system (Phillips Medical Systems, North America Company) with the image intensifier in the 9” fluoroscopic mode. Data from the 2 radiographic views were digitized and merged using custom software<sup>16,17</sup> to yield the 3-dimensional  $x,y,z$  coordinates for each of the radiopaque marker centroids every 16.7 seconds throughout the cardiac cycle. Ascending aortic pressure, LV pressure, and ECG voltage signals were digitized and recorded simultaneously on the marker images during data acquisition.

### Data Analysis

#### Hemodynamic and Cardiac Cycle Timing Markers

Two to 3 consecutive steady-state beats before (Preischemia) and during (Ischemia) proximal circumflex occlusion were averaged for each animal in the control (Control) and the Alfieri edge-to-edge repair (Alfieri) groups. For each cardiac cycle, end-systole (ES) was defined as the frame containing peak negative LV rate of pressure fall ( $-dp/dt$ ). End-diastole (ED) was defined as the videofluoroscopic frame containing the peak of the ECG R-wave. Instantaneous LV volume was computed from the subepicardial LV markers using a space-filling multiple tetrahedral volume method. Stroke volume was calculated as the difference between end-diastolic LV volume and end-systolic LV volume.

#### Mitral Annular, Leaflet, and Subvalvular Geometry

For each frame, MAA was computed from the 3-dimensional coordinates of the 8 markers sutured to the MA. After determining the annular centroid for the frame, the annular area was divided into 8 individual “pie slices,” which were summed to yield total annular area. The septal lateral (SL) annular diameter was calculated for each frame as the distance in 3-dimensional space between markers placed on the midanterior and midposterior MA, whereas the commissure-commissure (CC) annular diameter for the frame was determined as the distance between the 2 commissural markers. To assess leaflet tethering during ischemia, the orthogonal distance of each leaflet marker near the anterior and posterior commissures to the best fit (least squares) mitral annular plane was calculated for each frame throughout the cardiac cycle before and during ischemia in each group. The distance from the approximating stitch (force transducer) in the Alfieri group and the central leaflet coaptation point (mid-distance between the 2 central leaflet edge markers) in the Control group to the annular plane was also determined. In addition, the distances between the commissural leaflet edge marker pairs throughout the cardiac cycle were calculated for both experimental conditions in each group. Changes in subvalvular geometry were assessed by measuring the distance between the anterior (APM) and posterior (PPM) papillary muscle tip markers and calculat-

**TABLE 1. Hemodynamics in Both the Control and Alfieri Animals**

|                         | Control      |            | Alfieri      |            |
|-------------------------|--------------|------------|--------------|------------|
|                         | Pre-ischemia | Ischemia   | Pre-ischemia | Ischemia   |
| HR (min <sup>-1</sup> ) | 106±9        | 107±12     | 93±12#       | 89±10#     |
| LV dP/dt (mm Hg/s)      | 2,247±550    | 1,247±289* | 2,048±741    | 1,004±404* |
| ESV (ml)                | 107±26       | 146±34*    | 116±33       | 148±35*    |
| EDV (ml)                | 159±34       | 173±30*    | 148±27       | 174±38*    |
| SV (ml)                 | 35±12        | 27±12      | 32±16        | 26±7       |
| LVEDP (mm Hg)           | 11±5         | 21±11*     | 17±5#        | 24±7*      |
| LVESP (mm Hg)           | 65±13        | 52±10*     | 77±15        | 49±9*      |
| LVPmax (mm Hg)          | 109±9        | 84±11*     | 119±12       | 77±14*     |
| MR (+0-4)               | 0.5±0.4      | 1.9±0.7*   | 0.5±0.3      | 1.4±0.5*   |

HR=heart rate; LV dP/dt=maximum positive rate of change of LV pressure; ESV=end-systolic LV volume; EDV=end-diastolic LV volume; SV=stroke volume; LVEDP=LV end-diastolic pressure; LVESP=LV end-systolic pressure; LVPmax=maximum LV pressure; MR=mitral regurgitation.

\*P<0.05 vs. Pre-ischemia by t-test for dependent observations.

#P<0.05 vs. Control by t-test for independent observations.

ing PM “tethering,” defined as the distance from each PM tip to the midseptal annulus (ie, the annular saddle horn), before and during acute posterolateral ischemia.

**Statistical Analysis**

All of the data are reported as mean ± 1 SD, unless otherwise noted. Hemodynamic and marker-derived data from consecutive steady-state beats from each heart were aligned at ED. Marker data were calculated over 20 frames before and after ED, thus allowing evaluation over a period of 650 ms. The mean and SD for each variable at each sampling instant were computed for Preischemia and Ischemia in each group. Data were compared using Student’s t test for dependent (intragroup comparisons) and independent (intergroup comparisons) observations.

**Results**

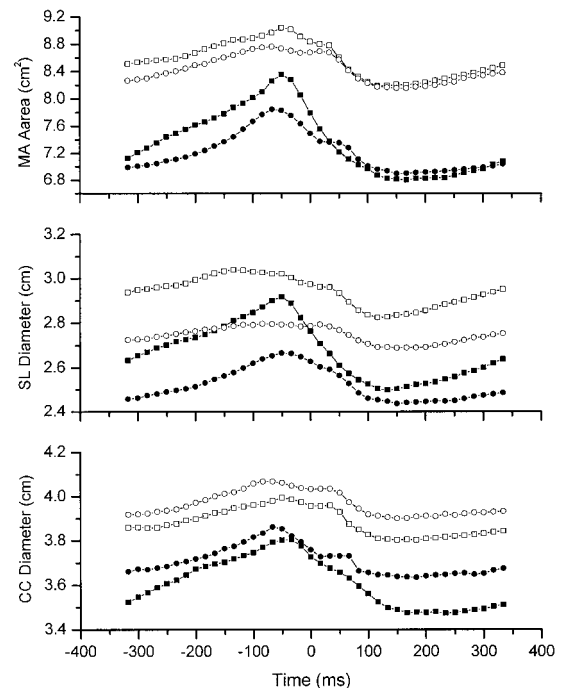
**Hemodynamics and Mitral Regurgitation**

Average animal weight (64±5 versus 68±5 kg, P=0.1), cardiopulmonary bypass time (79±10 versus 82±9 minutes, P=0.6), and aortic cross-clamp time (60±7 versus 61±7 minutes, P=0.8) did not differ between the 2 groups. Table 1 summarizes the hemodynamic variables in the Control and Alfieri groups before and during acute LV ischemia. In both groups, ischemia resulted in comparable changes in LV dP/dt, LV end-systolic and end-diastolic volume, LV end-diastolic and end-systolic pressure, as well as maximum LV pressure. Before induction of ischemia, the 2 groups differed only in heart rate and LV end-diastolic pressure. Thus, the animals were studied under reasonably similar hemodynamic conditions both before and during acute ischemia. Trace mitral regurgitation was present in both Control and Alfieri animals at baseline and increased significantly with proximal circumflex coronary artery occlusion in both groups (Table 1). There was no difference in the degree of IMR between the Control group and the Alfieri animals. IMR in the Control group was mostly central and holosystolic, whereas in the Alfieri group the regurgitant jets were observed in both orifices, on either side of leaflet approximation site.

**Annular and Subvalvular Geometry**

MAA, SL annular diameter, and CC annular diameter dimensions throughout the cardiac cycle before and during ischemia

in both groups are shown in Figure 3, with the end-systolic measurements summarized in Table 2. Ischemia resulted in a significant increase in annular area, SL diameter, and CC diameter in both groups, and the magnitude of increase at ES was similar (MAA- 21±15 versus 19±9%, SL- 12±6 versus 12±11%, CC- 9±5 versus 6±4%, for Control and Alfieri, respectively; P=NS for all). There were significant changes in subvalvular geometry induced by acute ischemia in both groups (Table 2). The distance between PM tips at ES increased substantially with ischemia in the Control and Alfieri animals (increase of 9.3±2.9 versus 8.0±3.9 mm for



**Figure 3.** MAA (top panel), septal-lateral annular diameter (middle panel), and CC diameter (bottom panel) throughout the cardiac cycle before (solid symbols) and during (open symbols) ischemia for Control (squares) and Alfieri (circles) groups. A 650 ms time interval centered at ED (t=0) is illustrated for both groups.

TABLE 2. Annular and Subvalvular Geometry at End-Systole in Both Groups

|                        | Control      |           | Alfieri      |           |
|------------------------|--------------|-----------|--------------|-----------|
|                        | Pre-ischemia | Ischemia  | Pre-ischemia | Ischemia  |
| MAA (mm <sup>2</sup> ) | 706±128      | 840±98*   | 713±103      | 850±123*  |
| SL (mm)                | 24.9±3.2     | 27.6±2.3* | 26.2±2.7     | 29.3±3.2* |
| CC (mm)                | 37.6±2.7     | 39.7±2.8* | 35.2±3.1     | 38.4±3.2* |
| APM-PPM (mm)           | 26.5±3.3     | 35.7±1.3* | 26.5±5.2     | 34.5±5.9* |
| APM-Saddle horn (mm)   | 48.9±3.5     | 49.9±3.4* | 43.9±4.7#    | 44.7±5.2# |
| PPM-Saddle horn (mm)   | 51.0±3.0     | 52.5±3.2* | 48.0±5.9     | 49.5±6.7* |

MAA=mitral annular area; SL=septal-lateral annular diameter; CC=commissure-commissure annular diameter; APM=anterior papillary muscle; PPM=posterior papillary muscle; saddle horn=middle of septal (fibrous) annulus.

\* $P<0.05$  vs. Pre-ischemia by t-test for dependent observations.

# $P<0.05$  vs. Control by t-test for independent observations.

Control and Alfieri, respectively;  $P=0.5$ ) The significant increase in distance from the PPM tip to the center of the anterior annulus (annular saddle horn) was also comparable in both groups ( $1.5\pm 1.3$  versus  $1.6\pm 1.4$  mm for Control and Alfieri, respectively;  $P=0.9$ ). The distance from the APM tip to the annular saddle horn increased significantly with ischemia in the Control group and was possibly larger ( $P=0.07$ ) in the Alfieri animals. Thus, the annular and subvalvular geometric perturbations associated with acute posterolateral ischemia were consistent and similar between the 2 groups. Although distance from the PPM tip to the annular saddle horn did not differ between the groups either before or during ischemia, the distance from the APM tip to the saddle horn was smaller in the Alfieri group (Table 2).

### Mitral Leaflets

Distances at ES between the leaflet edge markers near the anterior and posterior commissures and all leaflet edge markers away from the annular plane are summarized in Table 3. The distance between leaflet edge pairs increased with ischemia at both locations in both groups. There was no change with ischemia in the position of the anterior leaflet edge markers relative to the mitral annular plane in either the Control or Alfieri animals, whereas relative apical restriction (increased distance to the annular plane) and prolapse (decreased distance to the annular plane) were observed during ischemia for the posterior leaflet anterior and posterior commissure markers, respectively. The leaflet approximation point in the Alfieri group (marked by the miniature force transducer) was also displaced apically away from the annular plane with ischemia ( $5.3\pm 1.4$  versus  $6.5\pm 1.4$  mm for Preischemia and Ischemia, respectively;  $P=0.008$ ). The central leaflet coaptation point (calculated as the mid-distance between the 2 central leaflet edge markers) in the Control group was displaced to a similar degree with ischemia ( $5.8\pm 1.1$  versus  $7.0\pm 1.2$  mm for Preischemia and Ischemia, respectively;  $P=0.004$ ).

### Discussion

IMR continues to be a clinical challenge, and the best surgical treatment for this ever-increasing patient population remains to be defined. Alfieri edge-to-edge mitral repair along with mitral ring annuloplasty partially eliminates ischemic and

functional mitral regurgitation.<sup>10,12</sup> However, no large series of patients with IMR treated with this technique has been reported, and the efficacy of Alfieri repair without ring annuloplasty is unknown. This acute ovine experiment revealed that the Alfieri repair did not prevent acute IMR. Furthermore, it did not alter the annular, subvalvular, and leaflet geometric distortions associated with acute ischemia.

Acute posterolateral ischemia in sheep results in annular dilatation and larger SL annular diameter,<sup>18</sup> similar to that reported here. However, the mitral CC diameter increase, has not been observed previously and may be because of the acute, open-chest nature of this experiment. Interestingly, the annular geometric changes during ischemia did not differ between the Control and Alfieri groups. In particular, the magnitude of SL diameter dilation, which may be key in the development of acute IMR,<sup>4</sup> was similar, suggesting that leaflet approximation did not constrain this annular dimension in the double-orifice repair group. Displacement of PMs away from the annular saddle horn has been reported to be an independent predictor of mitral regurgitant volume,<sup>19</sup> and such displacement of both PM tips was observed in the Control group. With the Alfieri repair, the PPM was displaced away from the midseptal annulus (with a trend toward displacement of the anterior PM). Thus, changes in PM geometry normally associated with IMR were also seen in the Alfieri group, which may explain its ineffectiveness in reducing the degree of IMR. Although an experimental ovine study suggested that the Alfieri repair may satisfactorily correct alterations in subvalvular geometry seen with LV ischemia,<sup>13</sup> our data do not support that conclusion. This discordance may be because of the differences between acute and chronic models of IMR. It must be noted that the Alfieri edge-to-edge leaflet approximation did decrease the distance between the anterior PM tip and the annular saddle horn relative to Control, indicating some effect of the repair on subvalvular geometry. However, this alteration did not affect the geometric subvalvular perturbations normally seen with IMR.

Surprisingly, the leaflet changes found with acute ischemia were similar in the 2 groups despite central leaflet edge approximation in the Alfieri group. The increase in leaflet edge-edge distance during ischemia was consistent with previously published data from our laboratory in a closed-chest preparation.<sup>20</sup> However, it was unexpected that central

**TABLE 3. Leaflet Edge Distances at End-Systole**

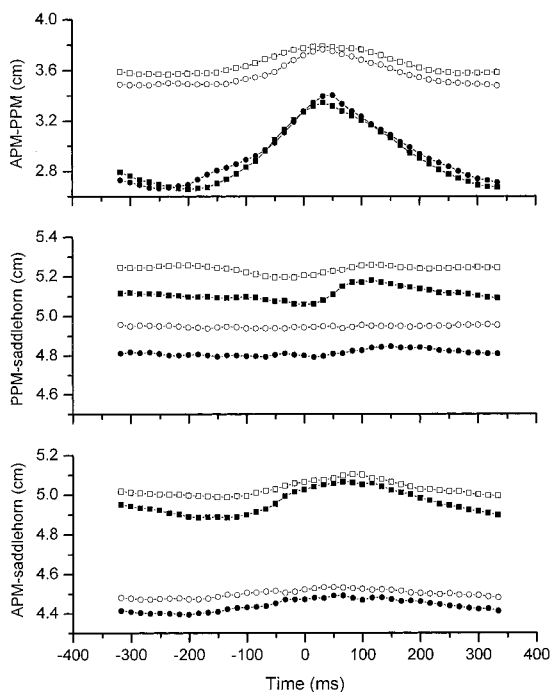
|  | Control      |          | Alfieri      |           |
|--|--------------|----------|--------------|-----------|
|  | Pre-ischemia | Ischemia | Pre-ischemia | Ischemia  |
| AML-PML <sub>ACOM</sub> (mm)               | 4.8±2.4      | 6.1±2.4* | 4.0±1.1      | 4.7±1.7*  |
| AML-PML <sub>PCOM</sub> (mm)               | 4.9±1.6      | 6.7±2.1* | 9.5±2.7      | 11.5±3.4* |
| AML <sub>ACOM</sub> -MA <sub>PL</sub> (mm) | 7.0±1.2      | 7.3±1.3  | 8.4±1.6      | 8.5±1.2   |
| AML <sub>PCOM</sub> -MA <sub>PL</sub> (mm) | 6.8±1.4      | 6.4±1.3  | 7.6±2.2      | 7.0±2.1   |
| PML <sub>ACOM</sub> -MA <sub>PL</sub> (mm) | 7.2±1.3      | 7.7±1.3* | 7.9±0.9      | 8.3±0.8*  |
| PML <sub>PCOM</sub> -MA <sub>PL</sub> (mm) | 6.7±0.8      | 6.0±0.9* | 6.1±1.4      | 5.6±1.2*  |

AML=anterior mitral leaflet; PML=posterior mitral leaflet; PCOM=posterior mitral commissure; ACOM=anterior mitral commissure; MA<sub>PL</sub>=least squares mitral annular plane.

\**P*<0.05 vs. Pre-ischemia by t-test for dependent observations.

leaflet attachment did not facilitate leaflet coaptation near the commissures during ischemia. Some investigators<sup>21</sup> have postulated that IMR results from subvalvular changes, and the present data are consistent with such a hypothesis. As annular enlargement seen with ischemia was not attenuated by the edge-to-edge repair, it is possible that increased leaflet edge separation was simply a reflection of increased annular SL diameter. Analysis of leaflet edge displacement from the mitral annular plane revealed that during ischemia posterior leaflet apical restriction was present near the anterior commissure, whereas relative prolapse was observed near the posterior commissure. Such ischemic perturbations of leaflet geometry were predicted previously by Gorman et al<sup>21</sup> based on the altered PM position induced by acute ischemia.

Failure of the Alfieri repair to alter the annular, subvalvular, and leaflet perturbations during acute ischemia makes one wonder if this procedure without a concomitant annuloplasty will be effective clinically. The double-orifice technique is currently used in the repair of IMR with ring annuloplasty to facilitate leaflet coaptation<sup>12</sup> or as a “bail out” maneuver when annuloplasty alone does not completely correct the regurgitation.<sup>11</sup> Annuloplasty prevents annular dilatation, especially in the SL dimension, and thereby minimizes acute IMR.<sup>22</sup> Implantation of an annuloplasty ring attenuates the geometric alterations in leaflet geometry caused by acute ischemia.<sup>23</sup> Whether annular remodeling with a ring also changes the abnormal subvalvular geometry remains to be shown, but data from patients with dilated cardiomyopathy suggest that this may be the case.<sup>24</sup> Isolated annular SL diameter reduction alters PM position during acute ischemia,<sup>25</sup> indicating that annular interventions have an influence on subvalvular geometry. It is likely that ring annuloplasty alone is sufficient to correct IMR in many cases, reserving the Alfieri repair as a possible bail out. Our data do not support use of the edge-to-edge repair as an isolated procedure for acute IMR, because it does not prevent IMR nor correct the annular, subvalvular, or leaflet geometric alterations. These findings are corroborated by recurrence of MR in patients with dilated cardiomyopathy who underwent partial ventriculectomy and mitral repair using an Alfieri stitch alone.<sup>10</sup> The current study also provides more insight into the complex pathophysiology of IMR and reinforces the notion that IMR affects the valvular-ventricular complex on multiple levels. Interventions that target these geometric perturbations in isolation will not be successful. Future studies are needed to clarify the complete pathogenesis of IMR.



**Figure 4.** Inter-papillary distance (top panel), posterior papillary muscle tip to annular saddle horn distance (middle panel), and anterior papillary muscle tip to annular saddle horn distance (bottom panel) throughout the cardiac cycle before (solid symbols) and during (open symbols) ischemia for Control (squares) and Alfieri (circles) groups. A 650 ms time interval centered at ED (t=0) is illustrated for both groups.

**Study Limitations**

The findings of this study must be interpreted in light of many limitations. The data were derived during acute ischemia used to induce IMR, which is distinctly different from chronic IMR seen in the clinical setting where ventricular dilatation and chamber remodeling may have much greater effects. The Alfieri repair was performed before the ischemic insult, which again departs from the clinical scenario. Leaflet approximation was used to prevent rather than correct IMR in healthy ovine hearts. Clinically, the Alfieri repair is often done in the location of the regurgitant jet, which may not

necessarily involve the central leaflets. It is possible that a more “custom tailored” leaflet approximation would have been more efficacious, although this seems unlikely based on the regurgitant jet location in the Control animals. Third, the use of a force transducer to affect the edge-to-edge repair does not simulate what is done clinically. These factors and this animal model preclude direct translation of these results to human subjects. Although anatomic differences may exist,<sup>26</sup> mitral valvular dynamics are similar in humans and sheep,<sup>27,28</sup> and reliable models of human cardiac pathophysiology have been established in the ovine model.<sup>29</sup>

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