Septal-lateral annular cinching abolishes acute ischemic mitral regurgitation

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Objective: Ring annuloplasty prevents acute ischemic mitral regurgitation in sheep, but it also abolishes normal mitral annular and posterior leaflet dynamics. We investigated a novel surgical approach of simple septal-lateral annular cinching with sutures to treat acute ischemic mitral regurgitation.

Methods: Nine adult sheep underwent implantation of multiple radiopaque markers on the left ventricle, mitral anulus, and mitral leaflets. A septal-lateral transannular suture was anchored to the midseptal mitral anulus and externalized to a tourniquet through the midlateral mitral anulus and left ventricular wall. Open-chest animals were studied immediately postoperatively. Acute ischemic mitral regurgitation was induced by means of proximal left circumflex artery snare occlusion, and 3 progressive steps of septal-lateral annular cinching (each 2-3 mm suture tightening for 5 seconds) were performed with the transannular suture. Biplane videofluoroscopy for 3-dimensional marker coordinates and transesophageal echocardiography were performed continuously before and during left circumflex ischemia and septal-lateral annular cinching.

Results: Acute left circumflex ischemia caused ischemic mitral regurgitation ($+0.5 \pm 0.4$ [baseline] vs $+2.0 \pm 0.7$ [ischemia]; $P = .005$; scale, $+0-4$), which decreased progressively with each step of septal-lateral annular cinching and was eliminated during the third step (ischemic mitral regurgitation, $+0.6 \pm 0.5$; $P =$ not significant vs baseline). The third step of septal-lateral annular cinching decreased the septal-lateral diameter by 6.0 ± 2.6 mm ($P = .005$); however, mitral anulus area reduction ($8.5\% \pm 1.0\%$ and $6.9\% \pm 1.9\%$ for ischemic mitral regurgitation and septal-lateral annular cinching step 3, respectively; $P = .006$) and posterior leaflet excursion ($50^\circ \pm 9^\circ$ and $44^\circ \pm 11^\circ$ for regurgitation and annular cinching step 3, respectively; $P = .002$) throughout the cardiac cycle were affected only mildly. Normal mitral annular 3-dimensional shape was maintained with septal-lateral annular cinching.

Conclusions: Isolated $22\% \pm 10\%$ reduction in mitral annular septal-lateral dimension abolished acute ischemic mitral regurgitation in normal sheep hearts while allowing near-normal mitral annular and posterior leaflet dynamic motion. Septal-lateral annular cinching may represent a simple method for the surgical treatment of ischemic mitral regurgitation, either as an adjunctive technique or alone, which helps preserve physiologic annular and leaflet function.

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Ischemic mitral regurgitation (IMR) continues to frustrate surgeons because neither its mechanism nor an ideal surgical therapy has been clearly defined. MR caused by ischemic heart disease is associated with a far less satisfactory prognosis than other forms of mitral disease.¹⁻³ Although mitral valve repair, usually consisting of simple ring annuloplasty, has been associated with more encouraging results in this challenging patient cohort,^{4,5} the superiority of valve repair over valve replacement has yet to be firmly established.^{6,7} Unfortunately, only approximately 50% of patients are still alive at 5 years, primarily because of left ventricular (LV) dysfunction present at the time of the operation caused by previous LV infarction and ischemia. Mitral ring annuloplasty has been demonstrated to effectively correct IMR in clinical⁷⁻⁹ and experimental¹⁰ studies, most likely by facilitating leaflet coaptation through reduction of the annular septal-lateral (SL; or clinically termed anteroposterior) dimension.¹⁰ On the other hand, ovine experiments have shown that ring annuloplasty, whether semirigid or flexible, abolishes normal mitral annular dynamics¹¹ and freezes the posterior mitral leaflet.¹² Limited posterior leaflet excursion after implantation of a rigid annuloplasty ring has also been reported in a porcine model¹³ and clinically is seen often after any type of annuloplasty.

We developed a novel technique of SL annular reduction using a simple transannular suture to enhance leaflet coaptation while avoiding the deleterious effects of ring annuloplasty on annular and leaflet dynamic motion. By using radiopaque marker technology, we carried out a preliminary investigation of the efficacy of septal-lateral annular cinching (SLAC) in an open-chest sheep preparation during acute posterolateral ischemia.

Methods

Surgical Preparation

Nine adult sheep were used in the study. The operative procedure for marker implantation has been described previously in detail.¹⁴ The markers were implanted on the left ventricle, around the mitral annulus, and on the central edge of each leaflet, as shown in Figure 1. A single 4-0 Prolene suture (Ethicon, Inc, Somerville, NJ) was anchored with Teflon felt pledgets at the midseptal (or anterior) annulus (annular saddle horn) and externalized through the midlateral (or posterior) annulus to a tourniquet on the epicardial surface (Figure 2). After completion of marker implantation, a silicone rubber loop was placed around the proximal left circumflex coronary artery for induction of posterolateral ischemia and IMR. Subsequently, the heart was defibrillated, and the animal was weaned from cardiopulmonary bypass and transferred immediately to the experimental animal catheterization laboratory, where the animals were studied while intubated with an open chest and anesthetized with ketamine ($1-4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ intravenous infusion) and diazepam (5 mg intravenous bolus as needed). Intravenous esmolol infusion ($20-50 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was used to minimize reflex sympathetic responses. Simultaneous biplane

Figure 1. Array of LV (circles), mitral annular (squares), and leaflet (triangles) markers used in this ovine experiment. AML, Anterior mitral leaflet; PML, posterior mitral leaflet.

videofluoroscopy, hemodynamic data, and transesophageal color Doppler echocardiography were recorded continuously during acute occlusion of the proximal circumflex artery (IMR) and 3 progressive steps of SLAC (SLAC-1, SLAC-2, and SLAC-3; each step being roughly 2-3 mm more suture tightening than the previous step and held for approximately 5 seconds).

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 the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council, and published by the National Academy Press, revised 1996. This study was approved by the Stanford Medical Center Laboratory Research Animal Review committee and conducted according to Stanford University policy.

Data Acquisition and Analysis

Data acquisition,¹⁴ digital transformation,¹⁵ and 3-dimensional reconstruction¹⁶ were performed as described previously. Two to 3 consecutive steady-state beats during IMR and each of the 3 steps of SLAC were designated as IMR, SLAC-1, SLAC-2, and SLAC-3 data for each animal, respectively. For each cardiac cycle, end-systole was defined as the frame containing the peak rate of fall of LV pressure ($-dP/dt$), and end-diastole as the videofluoroscopic frame containing the peak of the electrocardiographic R wave. Instantaneous LV volume was computed from the epicardial LV markers by using a space-filling multiple tetrahedral volume method.¹⁷ MR was graded subjectively by an experienced cardiologist (D.L.) according to the extent and width of the regurgitant jet and

Figure 2. Schematic illustration of the mitral valve with annular (squares) and leaflet (triangles) markers and the aortic valve included for orientation. SLAC suture (dashed line) spans the annular SL dimension and was externalized to an epicardial tourniquet. Arrow shows the direction of annular cinching. AV, Aortic valve; ACOM, anterior commissure; PCOM, posterior commissure; AML, anterior mitral leaflet; PML, posterior mitral leaflet.

categorized as none (0), mild (+1), moderate (+2), moderate to severe (+3), or severe (+4).

Mitral Annular Dynamics

Mitral annular area was computed from the 3-dimensional coordinates of the 8 markers sutured to the mitral anulus by using an annular centroid.¹⁰ The SL annular diameter was calculated as the distance in 3-dimensional space between markers placed on the midseptal and midlateral mitral anulus, and the commissure-commissure (CC) diameter was determined as the distance between the markers on the anterior and posterior commissures. Angular position of the anterior leaflet edge was calculated as the angle (θ_{AML}) between the anterior leaflet edge marker and the SL annular diameter.¹⁸ Posterior leaflet edge angular position (θ_{PML}) was calculated in similar fashion. Leaflet excursion was calculated from diastolic maximum to systolic minimum angle. For 3-dimensional reconstruction of mitral annular shape, a right-handed Cartesian coordinate system was used with the origin located at the midseptal anulus marker, with the Y-axis passing through the LV apex (positive toward the apex), with the positive X axis directed toward the midlateral anulus such that the midlateral marker was contained in the X-Y plane, and with the positive Z-axis directed toward the posterior commissure. The midseptal anulus was chosen as the origin because it is at the center of the fibrous anulus, the position and geometry of which are minimally affected by posterolateral LV ischemia.

Statistical Analysis

All data are reported as means $\pm$ 1 SD. Hemodynamic and marker-derived data from consecutive steady-state beats from each heart were time aligned at end-diastole. Marker data were calculated over 20 frames before and after end-diastole, thus allowing

TABLE 1. Hemodynamics

	Pre-IMR	IMR	P value*
HR (beats/min)	106 $\pm$ 9	106 $\pm$ 13	.9
dP/dt _{max} (mm Hg)	2385 $\pm$ 353	1265 $\pm$ 300	.0001
EDV (mL)	146 $\pm$ 25	170 $\pm$ 23	.007
ESV (mL)	108 $\pm$ 27	139 $\pm$ 18	.0002
SV (mL)	38 $\pm$ 7	30 $\pm$ 10	.2
LVEDP (mm Hg)	11 $\pm$ 5	18 $\pm$ 7	.009
LVP _{max}	110 $\pm$ 10	84 $\pm$ 12	.0001

Data are presented as mean $\pm$ SD.
HR, Heart rate; dP/dt_{max}, maximum positive rate of change of LV pressure; EDV, LV end-diastolic volume; ESV, LV end-systolic volume; SV, stroke volume; LVEDP, LV end-diastolic pressure; LVP_{max}, maximum LV pressure.
*Student *t* test for paired observations.

evaluation over a time period of 650 ms. The mean and SD for each variable at each sampling instant were computed for each condition. Data were compared by using repeated-measures analysis of variance, followed by the Student *t* test for paired observations when a significant F value was detected.

Results

Hemodynamics

The average weight of the animals used in the study was 65 $\pm$ 5 kg ($\pm$ 1 SD). The mean cardiopulmonary bypass time was 80 $\pm$ 9 minutes, and the mean aortic crossclamp time was 60 $\pm$ 7 minutes. Group mean hemodynamic parameters before and after induction of acute posterolateral ischemia are shown in Table 1. Peak LV dP/dt and LV pressure decreased, whereas LV end-diastolic and end-systolic volumes and end-diastolic pressure increased with proximal circumflex occlusion and IMR. No further statistically significant change in hemodynamic parameters was observed during continued ischemia and the SLAC steps, as shown in Table 2.

Mitral Regurgitation

Before circumflex occlusion, 3 animals had mild MR, 3 had trace MR, and 3 had no MR for a baseline average of +0.5 $\pm$ 0.4. The significant increase in the mean degree of MR during acute posterolateral ischemia and subsequent decreases with SLAC steps are summarized in Table 3. IMR was mostly central and holosystolic during circumflex occlusion. The final step of annular cinching completely abolished IMR because there was no difference in the degree of MR between SLAC-3 and the baseline value (+0.6 $\pm$ 0.5 and +0.5 $\pm$ 0.4, *P* = .6).

Mitral Annular Dynamics

Group mean data for mitral annular area and SL and CC diameters are tabulated in Table 3 and shown in Figure 3. Progressive annular SL reduction was accompanied by a corresponding reduction in mitral annular area and MR, with a small but significant increase in the mitral CC diam-

TABLE 2. SLAC hemodynamics

	IMR	SLAC-1	SLAC-2	SLAC-3
HR (beats/min)	106 ± 13	106 ± 12	107 ± 13	106 ± 12
dP/dt _{max} (mm Hg)	1265 ± 300	1262 ± 343	1217 ± 355	1298 ± 424
EDV (mL)	170 ± 23	169 ± 23	169 ± 23	168 ± 24
ESV (mL)	139 ± 18	140 ± 19	140 ± 18	139 ± 19
SV (mL)	30 ± 10	30 ± 9	29 ± 10	28 ± 11
LVEDP (mm Hg)	18 ± 7	19 ± 9	21 ± 10	22 ± 10
LVP _{max}	84 ± 12	84 ± 12	83 ± 16	81 ± 16

Data are presented as mean ± SD.

HR, Heart rate; dP/dt_{max}, maximum positive rate of change of LV pressure; EDV, LV end-diastolic volume; ESV, LV end-systolic volume; SV, stroke volume; LVEDP, LV end-diastolic pressure; LVP_{max}, maximum LV pressure.

TABLE 3. Mitral leaflet and annular dynamics

	IMR	SLAC-1	SLAC-2	SLAC-3	P value*
MR	+2.0 ± 0.7	+1.8 ± 0.7	+1.0 ± 0.4†	+0.6 ± 0.5†	.0005
SL _{ED} (mm)	27.7 ± 2.7	26.0 ± 3.4	24.5 ± 3.0†	21.7 ± 3.9†	.0005
CC _{ED} (mm)	40.1 ± 2.7	40.4 ± 2.7†	40.5 ± 2.6†	41.0 ± 2.7†	.0005
MAA _{ED} (mm ²)	856 ± 97	823 ± 110	798 ± 103†	737 ± 118†	.0005
MAA _{CONT} (%)	8.5 ± 1.0	8.0 ± 1.0	7.4 ± 0.9†	6.9 ± 1.9†	.005
Θ-PML _{EXC} (°)	50 ± 9	48 ± 10	47 ± 9	44 ± 11†	.0005
Θ-AML _{EXC} (°)	50 ± 5	50 ± 5	48 ± 6	48 ± 7	.30

Data are presented as mean ± SD.

SL_{ED}, End-diastolic mitral annular septal-lateral diameter; CC_{ED}, end-diastolic mitral annular commissure-commissure diameter; MAA_{ED}, end-diastolic mitral annular area; MAA_{CONT}, mitral annular area contraction during the cardiac cycle; Θ-PML_{EXC}, posterior mitral leaflet angular excursion with respect to the annular septal-lateral diameter; Θ-AML_{EXC}, anterior mitral leaflet angular excursion with respect to the annular septal-lateral diameter.

*Repeated-measures ANOVA.

†P < 0.016 (0.05/3) by Student t test for paired observation versus IMR.

eter during each SLAC step. During SLAC-3, a 22% ± 10% SL reduction was associated with reduction of MR to pre-ischemic levels. To abolish MR completely, however, the SL diameter had to be reduced to below its preischemic size (Figure 3). SLAC-3 reduction resulted in a 14% ± 7% decrease in total annular area, but annular area reduction throughout the cardiac cycle was only modestly smaller; thus, the dynamics of the annulus were reasonably well preserved. The 3-dimensional mitral annular geometry at end-diastole for IMR and SLAC steps is reconstructed in Figure 4. SLAC reduced the SL diameter by approximating the midlateral annulus (along with, to a lesser extent, the adjacent lateral annular segments) to the midseptal annulus. The mitral annulus maintained its saddle shape during IMR and SLAC.

Mitral Leaflet Dynamics

Group mean anterior and posterior leaflet edge angles during the cardiac cycle during IMR and SLAC are shown in Figure 5, with leaflet excursion, from diastolic maximum to systolic minimum, summarized in Table 3. There was no change in anterior leaflet excursion during progressive SLAC compared with IMR. Although posterior leaflet excursion was significantly decreased with SLAC-3, this de-

crease was only by 6° ± 4°, indicating that only a slight limitation of posterior leaflet motion was associated with this technique of annular SL reduction.

Discussion

IMR remains a challenging entity for surgeons. The valve is morphologically and structurally normal, but myocardial injury and dysfunction inherent in the pathophysiology of IMR adversely influence postoperative outcome.⁴ Ring annuloplasty can effectively correct IMR in many patients,^{7,8} but complete or partial, flexible or rigid annuloplasty rings abolish normal annular¹¹ and posterior leaflet dynamic motion.¹² In the current ovine experiment, SLAC with a simple transannular suture abolished acute IMR without markedly perturbing normal mitral annular dynamics and posterior leaflet motion.

Previous ovine experiments have suggested that annular dilatation may be the chief mechanism of acute IMR,¹⁹ although other experimental studies have identified changes in subvalvular geometry as playing the primary role in the genesis of IMR.²⁰⁻²² Ring annuloplasty prevents acute IMR in normal sheep by facilitating leaflet coaptation through reduction of the annular SL (anterior-posterior in clinical jargon) dimension¹⁰ because this is the principal direction of

Figure 3. Group mean data for SL annular diameter (in millimeters, *top*), mitral annular area (in square millimeters, *center*), and CC annular diameter (in millimeters, *bottom*) throughout the cardiac cycle before (*pre-IMR*) and during acute IMR and progressive SLAC (SLAC-1, SLAC-2, and SLAC-3). A 650-ms time interval centered at end-diastole ($t = 0$) is illustrated for all 4 groups.

annular enlargement during acute left circumflex artery ischemia.^{19,23,24} Annular enlargement caused by CC diameter increase, on the other hand, does not seem to lead to MR,²⁵ and in the current experiment a slight increase in CC diameter was actually observed with SLAC. Conversely, ring annuloplasty has also been shown to attenuate apical leaflet tethering in acute ovine IMR,²⁶ suggesting an influence on the subvalvular apparatus. It is possible that SLAC abolished IMR by altering subvalvular geometry, although annular SL reduction leading to improved leaflet coaptation is more likely the predominant mechanism. Central MR during myocardial ischemia, as seen in the current study, is more likely to be associated with annular dilatation,²⁷ and it is therefore not surprising that reduction of the annular SL dimension would correct this type of IMR. Clinically, sur-

gical therapy designed to increase leaflet coaptation, such as implantation of an undersized ring annuloplasty, is usually effective in ameliorating MR in patients with advanced dilated cardiomyopathy, either idiopathic or ischemic.²⁸ Furthermore, the extent of annular SL reduction may be a determinant of operative success in patients with IMR undergoing valve repair.⁸ Any technique that reduces the size of the mitral annulus, however, also changes the 3-dimensional geometric relationships between the annulus and subvalvular apparatus because these structures are tightly coupled.²⁹ Perhaps restoration of this perturbed relationship partially accounts for the efficacy of SLAC in this ovine model of acute IMR.

SLAC effectively abolished IMR, but this novel technique only mildly altered normal mitral annular geometry

Figure 4. Left, Group mean 3-dimensional reconstruction of the mitral annulus at end-diastole during acute IMR and subsequent progressive SLAC (SLAC-1, SLAC-2, and SLAC-3). Drop lines are shown for IMR and SLAC-3 data points in the apical-basal and SL planes as *solid* (IMR) and *dashed* (SLAC-3) lines. Right, Rotated view of each reconstruction to the approximate level of the annular plane viewed from the lateral to septal annulus to illustrate the 3-dimensional shape of the annulus. ACOM, Anterior commissure; PCOM, posterior commissure.

and dynamic motion. The 6-mm annular SL reduction with SLAC-3 is comparable with the degree of annular reduction needed to prevent IMR with either a flexible or semirigid annuloplasty ring,¹⁰ but SLAC-3 reduced end-diastolic annular area by only 14%, which is considerably less than the 30% to 35% annular area reduction associated with annuloplasty rings.¹¹ Even though annular area was significantly smaller with SLAC, the magnitude of this decrease was modest; perhaps it is smaller total annular size reduction that permits continued dynamic motion of the annulus in SLAC. Annular flexibility serves a dual role by aiding LV filling in diastole and by facilitating leaflet coaptation in late diastole-early systole by virtue of its sphincteric action.³⁰ Therefore, preservation of annular flexibility may have physiologic advantages, yet ring annuloplasty generally minimizes dynamic area change.¹¹ Although SLAC substantially decreased annular SL diameter and mitral area, the 3-dimensional saddle shape of the annulus remained intact, with elevation of the midseptal annulus (or saddle horn) above the annular plane. Recent finite-element analysis of annular shape suggests that this saddle-shaped configuration may have important implications for reducing systolic stress on the valve leaflets.³¹

Perturbed posterior leaflet motion has been observed after implantation of an annuloplasty ring in animal models^{12,13} and is frequently observed clinically on postoperative echocardiography. Indeed, annuloplasty rings, whether flexible or semirigid, freeze the motion of the posterior

leaflet, effectively converting the mitral valve into a single leaflet valve.¹² Although SLAC inhibited posterior leaflet excursion modestly, the posterior leaflet remained mobile. Whether maintained posterior leaflet motion offers an advantage in terms of effectiveness or durability of valve repair remains to be determined. This could possibly distribute systolic closing stresses more favorably in a bileaflet valve, but further studies are needed to answer this question.

This experiment assessed a novel technique to reduce mitral annular SL dimension to enhance leaflet coaptation and correct IMR in an ovine model of acute ischemia. Progressive SLAC decreased MR because the SL diameter was cinched smaller, yet annular dynamics and posterior leaflet motion were only modestly affected. SLAC potentially represents an expedient and simple surgical method for the treatment of IMR, either alone or as an adjunctive technique.

Although SLAC was effective in abolishing IMR in this experiment, this model of acute IMR is distinctly different than the clinical situation consisting of chronic MR and LV dilatation and systolic dysfunction, which makes clinical extrapolation difficult. The above findings can only be interpreted in the setting of acute LV ischemia in a normal sheep heart under open-chest conditions. These observations cannot be applied to patients with chronic IMR under closed-chest conditions in which subvalvular geometric perturbations may play a more predominant role in the pathogenesis of MR. We are currently exploring a protocol of

Figure 5. Group mean data for angular displacement of the anterior mitral leaflet (*top*) and posterior mitral leaflet (*bottom*) throughout the cardiac cycle before (*pre-IMR*) and during acute IMR and progressive SLAC (SLAC-1, SLAC-2, and SLAC-3). Leaflet edge angular displacement was calculated with respect to the line between the midseptal and midlateral annulus. A 650-ms time window centered at end-diastole ($t = 0$) is shown.

chronic ovine IMR to validate the efficacy of SLAC in a more clinically relevant setting. Nonetheless, these preliminary findings can provide valuable surgical insight into the mechanisms and treatment of IMR and serve as a foundation for future studies. The myocardial marker method requires suturing small metal markers to intracardiac structures, but echocardiographic studies suggest that the markers do not interfere with mitral annular or leaflet motion because they are very small (aggregate mass = 20 ± 6 mg). Although there are many limitations inherent in this particular animal model, reliable models of cardiac pathophysiology have been established in ovine models.^{32,33}

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Discussion

Dr Irving L. Kron (Charlottesville, Va). Dr Timek, the mechanism you have created obviously is an acutely ischemic model, and this is a very interesting approach. I know your laboratory knows more about IMR than probably anyone on earth. The typical patient, obviously, has some retraction of the posterior leaflets, some scarring, annular dilatation, and such. Would this technique or some adaptation of it work in those situations, do you think?

Dr Timek. Thank you for that question. That is a very good point. This is an acute model in healthy, normal sheep, and therefore it does not reflect the clinical situation, where chronic changes and volume overload are present. However, this model gives us some insight into the mechanisms of IMR. We are currently working on a model of chronic ovine IMR, and we will try to investigate this method in that setting, which will be more clinically pertinent.