Edge-to-Edge Mitral Repair

Tension on the Approximating Suture and Leaflet Deformation During Acute Ischemic Mitral Regurgitation in the Ovine Heart

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**Background**—Edge-to-edge approximation of the mitral valve leaflets (Alfieri procedure) is a novel surgical treatment for patients with ischemic mitral regurgitation (IMR). Long-term durability may be limited if abnormal mitral leaflet stresses result from this procedure. The aim of the current study was to measure Alfieri stitch tension ($F_A$) and to explore its geometric determinants in an ovine model of acute IMR as a reflection of the mitral leaflet stresses imposed by the procedure.

**Methods and Results**—Eight sheep were studied immediately after surgical placement of (1) a force transducer interposed between sutures approximating the central leaflet edges and (2) radiopaque markers around the mitral annulus and leaflet edges. Computer-aided analysis of videofluorograms was used to obtained 3D marker coordinates. Simultaneous measurements of $F_A$, septal-lateral annular dimension ($L_{SL}$), leaflet edge separation ($L_{SEP}$), anterior ($L_{AL}$) and posterior ($L_{PL}$) leaflet length, and hemodynamic variables were obtained at baseline (CTL) and during acute IMR (circumflex artery occlusion). $F_A$ was significantly elevated throughout the cardiac cycle during IMR compared with CTL, with maximum $F_A$ in diastole ($0.26 \pm 0.05$ versus $0.46 \pm 0.08$ N, CTL versus IMR; $P<0.05$). Multivariable analysis revealed $L_{SL}$ as the single independent predictor of maximum $F_A$ ($P<0.001$). Positive linear correlations were shown between values of $F_A$ and $L_{AL}$ and $L_{PL}$ (dependent variables).

**Conclusions**—These experimental data demonstrate higher $F_A$ during IMR and cyclic changes in $F_A$ closely paralleling changes in $L_{SL}$, eg, being greatest in diastole when the annulus is largest. Increased $F_A$ during IMR is probably indicative of successful therapeutic intent, but higher diastolic leaflet stresses resulting from persistent or progressive mitral annular dilatation may adversely affect repair durability. This indirectly implies that concomitant mitral ring annuloplasty should be added to the Alfieri repair. (Circulation. 2001;104[suppl I]:I-29-I-35.)

**Key Words:** mitral valve • valvuloplasty • coronary disease

Mitral valve repair has become the preferred method for correcting ischemic mitral regurgitation (IMR). It provides durable and predictable results in most patients and probably superior clinical outcomes compared with mitral valve replacement. Mitral annuloplasty, with either a prosthetic ring or suture plication, has been applied to correct IMR with the intent of reducing mitral annular area and improving leaflet apposition. Ring annuloplasty has also been shown to prevent IMR in an ovine model of acute LV ischemia, but ring annuloplasty abolishes normal mitral annular dynamics and restricts posterior leaflet mobility. Ring annuloplasty alone, however, can be unpredictable in some patients with IMR.

Recently, a simple mitral valve repair method in which the leading edges of the mitral leaflets are approximated by use of a suture (Alfieri procedure or “bow-tie” repair) was introduced by Alfieri and colleagues. The technique involves short aortic cross-clamp times, and the location of the suture can be customized on the basis of the location of the regurgitant jet with both central and paracommissural leaflet approximation. The procedure has been shown to provide predictable and durable control of MR in patients with a wide spectrum of valvular pathology and was used successfully in a small series of patients with IMR. From theoretical models of the normal mitral valve, it is thought that the tension on the approximating suture between the mitral valve leaflet edges is close to zero. Long-term durability, however, may be limited in mitral valve diseases with preexisting deformation of the mitral valve apparatus if abnormal leaflet stresses result from the procedure.
In evaluating the Alfieri procedure in an ovine model of acute IMR, we hypothesized that mitral annular dilatation during IMR would significantly increase Alfieri stitch tension (F_A) and consequently augment stresses on the mitral valve leaflets. Therefore, the present study was performed to assess mitral leaflet stresses imposed by the procedure and to explore the geometric determinants of F_A in this experimental setting of acute IMR.

Method

Surgical Preparation

The surgical procedures used have been previously described. Adult sheep were used in the study. A diagram of the study protocol is shown in Figure 1. With the chest open but before marker implantation and mitral repair, the proximal circumflex coronary artery was dissected from the surrounding myocardium, and a silicone rubber snare occluder was placed proximal to the first obtuse marginal branch. Doppler echocardiography was used to determine the presence of acute IMR in all animals after a 2-minute occlusion of the proximal circumflex artery. Subsequently, 8 miniature radiopaque markers were inserted into the subepicardium of the left ventricle along 4 equally spaced longitudinal meridians with 2 levels between the left ventricular (LV) apex and base and 1 marker at the LV apex. After establishment of cardiopulmonary bypass and with the heart arrested, 8 markers were sutured around the circumference of the mitral annulus (1 near each commissure and 3 along the anterior and posterior annuli). Subsequently, the central edges of the anterior and posterior mitral leaflets were approximated with a 5-0 polypropylene suture reinforced with 2 small Teflon-felt pledgets as shown in Figure 2A and 2B. The approximating suture (Alfieri stitch) was placed &–5 mm from each leaflet edge and secured a miniature force transducer that served as another radiopaque marker (No. 13 in Figure 2B). The force transducer was constructed of a slit copper ring 5 mm in diameter and 0.4 mm thick. On each side of the slit, 2 small holes were incorporated to permit suture fixation. The transducer was used to connect a semiconductor strain gauge connected in a quarter-bridge electrical circuit. Technical specifications of the transducer have been described previously. Four additional radiopaque markers were placed on the posterior and anterior leaflet edges at the center of each of the 2 newly created valve orifices. Micromanometer-tipped catheters (Millar SPC-500) were placed in the LV chamber via the apex and in the left atrial lumen via the atriotomy for monitoring of hemodynamic measurements. Left atrial pressure (LAP) was measured via a transseptal approach, as described previously. The sheep were allowed to stabilize 3 to 5 minutes between data acquisition runs. The extent of MR during acute proximal circumflex occlusion after the edge-to-edge repair was compared with the extent of MR induced by circumflex occlusion before marker implantation and valve repair, thus allowing evaluation of the efficacy of the Alfieri stitch in the setting of acute IMR.

Data Acquisition

Videofluoroscopic images were acquired with the animals in the right lateral decubitus position (with the chest open) with a Philips Optimum 2000 biplane Lateral ARC 2/Poly DIAGNOST C2 system (Philips Medical Systems, North America) with the image intensifier in the 9-in fluoroscopic mode. Data from the 2 radiographic views were digitized and merged by use of custom-designed software to yield the images for each of the radiopaque markers every 16.7 seconds throughout the cardiac cycle. Ascending aortic pressure, LVP, LAP, F_A, and ECG voltage signals were digitized and recorded simultaneously during data acquisition.

Data Analysis

Hemodynamic and Cardiac Cycle Timing

Two or three consecutive steady-state beats during control and after occlusion of the circumflex artery were averaged and defined for each animal as CTL and IMR, respectively. In each cardiac cycle, end systole was defined as the frame containing peak rate of LVP fall (-dP/dt). End diastole was defined as the videofluoroscopic frame containing the peak of the ECG R wave. Instantaneous LV volume at end systole and end diastole was calculated from epicardial LV markers by use of a space-filling multiple tetrahedral volume method. Although myocardial volume is included in this calculation of LV volume, it accurately reflects changes in LV chamber size.

Mitrail Annular Dynamics

Mitrail annular area throughout the cardiac cycle was computed from 3D coordinates of the markers sutured around the mitral annulus (markers 1 through 8, Figure 2B). The mitral annular centroid was first calculated, and then the annular area was divided into 8 individual “pie slices” whose areas were summed to yield total annular area. The septal-lateral mitral annular diameter (D_SL) was determined as the distance in 3D space between markers placed on the midseptal and midlateral (posterior) mitral annuli (1 through 5 in Figure 2B). Mitral Valve Dynamics

The anterior and posterior mitral leaflet lengths (L_AL and L_PL, respectively) throughout the cardiac cycle were calculated as the 3D distances from the Alfieri stitch at the leaflet edges to the anterior and posterior leaflet bases, respectively (1–13 and 5–13, Figure 2B). Leaflet separation in the 2 newly created mitral orifices was computed as the distance between the respective leaflet edge markers (9–10 and 11–12, Figure 2). L_EDD was defined as the average of the distances between the leaflet edge markers in the 2 orifices.
Statistical Analysis

All data are reported as mean±SEM unless otherwise noted. Hemodynamic and marker-derived data from consecutive steady-state beats from each heart were time aligned at end systole. Marker data were calculated from 20 frames before to 20 frames after end systole, a duration of 650 ms. Differences between variables (Fₐ, L₅₋₇, LSEP, L₉₋₁₁, L₀₋₁₀) during CTL and IMR were compared at end diastole, end systole, peak Fₐ in diastole, and their minimum and maximum by use of a multivariate ANOVA with variables of time, before versus after circumflex artery occlusion, and sheep identification. Statistical significance was inferred if P<0.05.

Consecutive diastolic values of the transvalvular pressure gradient (LAP²LVP), L₅₋₇, LSEP, and CTL/IMR were entered into a general linear model multivariable analysis with Fₐ as the dependent variable. Because of the variability between animals, analysis was performed for each animal, and tests of significance of the regression coefficients (different from zero) were subsequently performed with the use of the ensemble of data from all experiments. Relationships between L₅₋₇, LSEP, and LAP−LVP (independent variables) and Fₐ (dependent variable) with caval occlusion at CTL and during IMR were tested at their maximum in diastole, at time of maximum Fₐ, and at end systole in similar linear regression models. Sheep identification was treated as a model factor to reduce the influence of animal-to-animal variability on the analysis. With the use of linear regression analysis, correlations between values at maximum Fₐ of L₅₋₇ and L₀₋₁₀ (dependent variables) and Fₐ (independent variable) during vena caval occlusion at CTL and IMR were tested for each experiment and all experiments together (see above). Statistical models in StatView 227 were used for the analysis.

Results

The average weight of the animals was 68±5 kg. The total duration of cardiopulmonary bypass was 82±9 minutes, with a mean aortic cross-clamp time of 61±7 minutes. Proper marker position and integrity of the leaflet-approximating stitch were confirmed in all animals at postmortem examination (Figure 2A).

Hemodynamics and MR

Hemodynamic variables after the edge-to-edge repair at CTL and during IMR are shown in Table 1. As expected, myocardial ischemia decreased LVP and dP/dtₘₜₜ and increased LV volumes and mitral annular area at end systole and end diastole. Figure 3 shows the degree of MR for each animal at CTL and IMR before and after the Alfieri procedure. The
location of the regurgitant jet was broadly central and holosystolic before the Alfieri repair, with some animals having additional smaller commissural jets. In most animals, IMR persisted after the repair, and the location of the jet was predominantly central (on both sides of the approximating stitch). As indicated by the thin lines in Figure 3, occlusion of the circumflex artery caused moderate MR in most animals. Heavy lines demonstrate the change in IMR before and after the Alfieri procedure. Except for 1 animal that had grade III MR after the edge-to-edge repair (possibly because of leaflet distortion from the transducer), the Alfieri procedure in general had a small effect on the degree of IMR (grade 1.5 ± 0.3 after the Alfieri procedure versus grade 1.8 ± 0.1 before the procedure, P = 0.4). Thus, it is important to note that in the setting of the Alfieri repair, acute occlusion of the proximal circumflex artery still resulted in significant IMR in this ovine preparation. In addition, there was no relationship between Alfieri stitch tension and the degree of MR during occlusion of the circumflex artery or between the change in Alfieri stitch tension and MR from CTL to IMR.

### Alfieri Stitch Tension

The time course of $F_A$, LVP, $L_{S-L}$, and $L_{SEP}$ at CTL and IMR (mean of 8 animals) at steady state and during vena caval occlusion at CTL and during IMR is shown in Figure 4. $F_A$ was significantly elevated throughout the cardiac cycle during IMR compared with CTL. Differences in $F_A$ between the 2 conditions compared at peak $F_A$ in diastole, at minimum $F_A$ in early systole, and at end systole were all statistically significant (Table 2), although the increase in tension was most remarkable in late systole with maximum $F_A$ increase at end systole. The change in $F_A$ from end systole to maximum in diastole was the same during IMR and CTL (0.18 ± 0.02 versus 0.12 ± 0.05 N, P = NS).

| TABLE 1. Hemodynamics and Mitral Annular Dimensions |
|---------------------------------------------|-----------|-----------|
| Heart rate, bpm                             | 95±5 (75–109) | 95±5 (79–118) |
| LVP$_{max}$, mm Hg                          | 121±5 (101–137) | 83±17 (65–121)* |
| LV + dP/dt$_{max}$, mm Hg/s                 | 1.6±0.2 (1.0–2.5) | 0.9±0.2 (0.36–1.48)* |
| LAP–LVP$_{max}$, mm Hg                      | 3.9±0.6 (0.9–6.3) | 2.5±0.6 (0.1–4.2)* |
| LW$_{LV}$, mL                               | 150±9 (116–196) | 177±26 (135–244)* |
| LW$_{LV}$, mL                               | 119±12 (82–172) | 153±13 (125–191)* |
| MA$_{AA}$, mm$^2$                           | 800±70 (580–1060) | 860±50 (670–1130)* |
| MA$_{AE}$, mm$^2$                           | 720±40 (590–890) | 820±50 (650–1040)* |

LW indicates left ventricular volume; ED, end diastole; ES, end systole; LV + dP/dt$_{max}$ = maximum rate of LVP rise; and MA, mitral annular area. Data are expressed as mean ± SEM with range (minimum to maximum) in parentheses.

*P < 0.05 vs CTL by t test for paired observations.

Figure 3. Doppler echocardiographic assessment of severity of mitral regurgitation (grades 0 through IV) at CTL and ischemia (IMR) before and after Alfieri procedure. Thin lines indicate change in mitral regurgitation resulting from myocardial ischemia; heavy lines, change in IMR before and after edge-to-edge repair.

Figure 4. Time course of $F_A$, LVP, $L_{S-L}$, and $L_{SEP}$ at CTL (squares) and IMR (triangles) at steady state (CTL-1, IMR-1) and during vena caval occlusion (CTL-2, IMR-2). Group mean data of 8 experiments are shown. Data are centered at end systole (time = 0 ms).
Correlates of Alfieri Stitch Tension

The time course of $F_A$ at CTL and IMR was closely related to cyclic changes in $L_{S-L}$. Maximum $F_A$ was found in diastole coincident with maximum $L_{S-L}$ and before maximum $L_{SEP}$. $F_A$ decreased during middiastole before the closing motion of the mitral leaflets. In most hearts, minimum $F_A$ occurred in early systole at the same time as minimum $L_{S-L}$. In 4 animals, the $F_A$ curves in diastole were bimodal with second peaks at end diastole, which explains the observed end-diastolic “humps” in the mean curves. Graphically, the $F_A$ curves closely paralleled changes in $L_{S-L}$ but did not appear to be related to changes in $L_{SEP}$ or the transvalvular pressure gradient. $L_{S-L}$ was also significantly higher during IMR compared with CTL, whereas $L_{SEP}$ was virtually unchanged before and after ischemia. $F_A$ and $L_{S-L}$ decreased during vena caval occlusions at CTL and during IMR, but $L_{SEP}$ remained almost unchanged (Figure 4).

In multivariate linear regression analysis, values of $F_A$ in diastole (versus corresponding values of $L_{S-L}$, $L_{SEP}$, and LAP−LVP) were significantly correlated to $L_{S-L}$ (the only statistically significant factor was regression coefficient, $\beta=0.014$ to 0.086 N/mm; $R^2=0.54$ to 0.97; $P<0.05$ in all animals). Multivariate linear regression analysis of relationships between maximum $L_{S-L}$, $L_{SEP}$, and LAP−LVP (independent variables) and maximum $F_A$ (dependent variable) during steady state and vena caval occlusions at CTL and IMR showed that maximum $L_{S-L}$ was the single statistically significant predictor of $F_A$ in all hearts ($P<0.001$). Values at maximum $F_A$ and at end systole of $L_{S-L}$, $L_{SEP}$, and LAP−LVP (independent variables) at CTL and during IMR (steady state and caval occlusions) were also entered into the model with corresponding values of $F_A$ as the dependent variable. In both analyses, $F_A$ was positively correlated with $L_{S-L}$ and $L_{SEP}$; however, in multivariable tests for each experiment, statistical significance fell out to either of the covariates, which indicates interaction between the factors.

Relation Between Alfieri Stitch Tension and Mitral Leaflet Deformation

Figure 5 illustrates the relationship between $F_A$ and $L_{AL}$ and $L_{PL}$ (mean of 8 experiments) from the time of minimum to maximum $F_A$ at CTL and during IMR. Positive statistically significant correlations were demonstrated between maximum $F_A$ and $L_{AL}$ and $L_{PL}$ (dependent variables) at CTL and IMR (steady state and caval occlusion) in each experiment ($L_{AL}$ versus $F_A$: $\beta=3.0$ to 39.4 mm/N, $R^2=0.57$ to 0.97, $P<0.05$ in all hearts; $L_{PL}$ versus $F_A$: $\beta=1.2$ to 17.8 mm/N, $R^2=0.51$ to 0.79, $P<0.05$ in all hearts) and for all animals together ($P<0.001$).

Discussion

Mitral valve reconstruction has become the procedure of choice for patients with most forms of mitral regurgitation. The Alfieri edge-to-edge repair as an adjunctive technique to correct IMR may be a valuable addition to the surgeon’s armamentarium for selected patients who otherwise would require more complicated repair techniques or replacement of a morphologically normal valve. Several advantages make the Alfieri repair appealing: As an adjunctive technique for repair of IMR, the Alfieri stitch can reduce the risks associ-
Zielinski and associates evaluated mitral valve replacement in this high-risk population. The Alfieri technique involves short aortic cross-clamp times and can be customized to the location of the regurgitant jet. Our previous ovine studies attributed acute IMR to annular dilatation and leaflet tethering, and most likely, both mechanisms contributed to the genesis of IMR in the current experiment. Although annuloplasty rings prevent acute ovine IMR, the mechanisms responsible for the clinical efficacy of annuloplasty rings in chronic IMR remain incompletely understood. An Alfieri stitch prevents leaflet separation and creates apposition of the mitral leaflets at that site; it can be a valuable “bail-out” procedure when ring annuloplasty fails to correct IMR satisfactorily. The edge-to-edge repair is intended to counteract leaflet tethering and incomplete mitral leaflet coaptation, which is considered to be a mechanism of IMR in patients. In the present study, acute occlusion of the circumflex artery still resulted in significant IMR even after the Alfieri repair, and there was no relationship between the magnitude of Alfieri stitch tension and the success of the repair. It is important to note, however, that the biomechanical approach of this study was not designed to evaluate the efficacy of the procedure in terms of valvular regurgitation (see Study Limitations).

Some cardiac surgeons have been understandably skeptical of the durability of a single-suture repair in an area of apparently high stress in which high systolic pressure gradients, rapid motion of the mitral leaflets in diastole, and alterations of the mitral valve attachments may potentially contribute to increased stresses on the thin valvular leaflet tissue. In this ovine model of acute IMR, LSEP was the major predictor of Alfieri stitch tension. Accordingly, the time course of Fₐ, with maximum in diastole, was closely related to cyclic changes in LSEP. Increased LSEP resulting from annular dilatation during acute ischemia resulted in higher Fₐ compared with CTL, with maximum Fₐ on the order of 16 to 70 g force. In comparison, the maximum systolic tension of a single chorda tendinea is in the range of 80 to 90 g force. Maximum Fₐ occurred before maximum LSEP, but the observed correlation between Fₐ and LSEP at maximum Fₐ in diastole suggests that the opening motion of the mitral leaflets may exert additional stresses on the Alfieri stitch. Mitral annular dynamics during CTL and IMR in this short-term open-chest study are similar to those observed in our previous conscious, closed-chest ovine experiments (7 to 11 days after annular marker implantation) and other published data.

In 10 very ill patients undergoing edge-to-edge mitral valve repair resulting from IMR, Umana et al anticipated that the mitral leaflets are naturally pushed together and that therefore stresses on the approximating stitch would not be excessive in systole when the suture serves mainly to limit the excursion of the leaflets into the left atrium during high LVP in systole. Consequently, they postulated that there would likely be less tension on the leaflet-approximating suture during systole. From a mathematical model of the stresses on the closed mitral valve derived by Arts et al, it was proposed that a decrease in annular diameter caused by insertion of a mitral annuloplasty ring reduces the leaflet surface area exposed to the systolic ventricular pressure and results in decreased tension on the edges of the leaflets and therefore on the suture. In accordance with this theory, the present study demonstrated lower Alfieri stitch tension with no relation to LVP in systole. Greater Alfieri stitch tension was seen in diastole, which was directly related to mitral annular dimensions at CTL during acute myocardial ischemia after circumflex artery occlusion in sheep without valve repair. Therefore, any increase in Alfieri stitch tension caused by residual or progressive annular dilatation may adversely affect repair durability.

Study Limitations

The major limitations of this study are those inherent in the acute animal model used. The study was based on experiments using acute myocardial ischemia and therefore did not take into account long-term changes, such as LV remodeling and resultant compensatory changes in the mitral subvalvular apparatus. Furthermore, although the extent of myocardial ischemia after circumflex artery occlusion has been shown to be very reproducible, the effect on mitral valve competency is not simple because it involves many components of the...
mitral valvular-ventricular complex. Therefore, these data must be interpreted in the setting of experimental acute IMR and cannot be extrapolated directly to chronic IMR in human subjects. The animals used in this study were anesthetized and studied in open-chest conditions, and no annuloplasty rings were used, all of which limit extrapolation of these experimental results to humans. Anatomical differences between ovine and human mitral leaflets and annulus must also be considered.

Because one of the goals of this study was to investigate leaflet and annular dynamics after the edge-to-edge repair, ring annuloplasty was purposely avoided. In addition, the approximating suture was placed centrally in the mitral orifice in all hearts even though prerepair Doppler echocardiography during ischemia revealed IMR with small regurgitant jets directed toward either of the commissures in some animals, findings that might have prompted a repair not located in the center of the valve. It should also be mentioned that performing the edge-to-edge repair and then inducing acute IMR is distinctly different from the clinical situation in which a broad leak may be present all along the leaflet coaptation zone. Furthermore, the presence of a force transducer might have compromised leaflet apposition adjacent to the approximation point and thereby worsened IMR. The lack of other control animals, ie, sheep without any repair (for comparison with normal annular dynamics) or a group with an Alfieri repair in combination with ring annuloplasty, presents further limitations. The mitral annular dynamics observed in the present study are concordant with our previous investigations of ovine mitral annular dynamics.

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References

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