Effect of Chronotropy and Inotropy on Stitch Tension in the Edge-to-Edge Mitral Repair

Tomasz A. Timek, MD; Sten L. Nielsen, MD; David T. Lai, FRACS; David Liang, MD, PhD; George T. Daughters, MS; Neil B. Ingels, Jr, PhD; D. Craig Miller, MD

Background—Our prior studies suggest that mitral annular septal-lateral (SL) diameter is the chief determinant of “Alfieri stitch” tension, but hemodynamic parameters may also play a role. We approximated the central edge of the mitral leaflets with a miniature force transducer to measure tension (T) at the leaflet approximation point during inotropic and chronotropic stimulation.

Methods and Results—Eight sheep were studied under open-chest conditions immediately after surgical placement of a miniature force transducer to approximate the leaflets and implantation of radiopaque markers on the LV and mitral annulus (MA). Chronotropic stimulation was induced with atrial pacing at 130 minutes⁻¹ (n=5) whereas inotropic state was increased with IV CaCl₂ bolus (n=8). Hemodynamic data, stitch tension, and 3-D marker coordinates were obtained throughout the cardiac cycle before and during each intervention. Peak stitch tension (TMAX) under all conditions was observed in diastole and temporally correlated with peak annular SL (SLMAX) size. Atrial pacing did not change peak transducer tension or annular size. Calcium infusion also did not alter peak transducer tension (0.29±0.11 versus 0.32±0.10 N; P=NS) and only slightly reduced SL dimension (29.9±3.3 versus 29.3±3.5 mm; P<0.05).

Conclusion—Isolated increase in heart rate or inotropic state did not alter peak stitch tension whereas enhanced contractile state decreased SL diameter minimally. These data, combined with those from our previous study, suggest that geometric (SL diameter) rather than hemodynamic parameters are the main determinants of “Alfieri stitch” tension. This implies that any interventional or surgical edge-to-edge repair performed without concomitant annular reduction to limit the SL dimension could expose the leaflet junction to forces which could limit repair durability. (Circulation. 2007; 116[suppl I]:I-276–I-281.)

Key Words: mitral valve ▪ valvuloplasty ▪ valves

Open surgical mitral valve reparative techniques continue to evolve¹ and provide durable and predictable results that represent superior clinical therapy relative to valve replacement.² The Alfieri edge-to-edge mitral repair is a recent simple addition to the evolving surgical armamentarium. This technique, in conjunction with ring annuloplasty, has been successfully applied to correct various etiologies of mitral insufficiency,³–⁶ even in patients with challenging mitral pathology.⁷,⁸ The procedure also lends itself to minimally invasive methods, and beating heart⁹ and percutaneous¹⁰ edge-to-edge mitral repair has been described in animal models and clinical trials of catheter-based repair are ongoing.¹¹ Interventionsal techniques, however, do not include mitral annular (MA) reduction which may limit repair durability as omitting a ring annuloplasty during surgical Alfieri repair has been associated with suboptimal results.¹² It is believed that annular reduction may relieve the stresses on the approximating suture and optimize the repair, yet the determinants of Alfieri stitch tension have not been completely characterized. Our prior ovine experiments in the same animals found annular septal-lateral diameter to exert the greatest influence on stitch tension,¹³,¹⁴ but in vitro experiments suggest that hemodynamic parameters predominate.¹⁵ In light of the expanding percutaneous application of the edge-to-edge repair, it is important to better define the geometric and hemodynamic factors which affect leaflet junction tension to provide reliable and durable clinical outcomes. In the analysis, inotropic and chronotropic stimulation was investigated to assess the effects of varying hemodynamic conditions on tension measurements of a miniature force transducer used to approximate the central edges of the mitral leaflets simulating clinical edge-to-edge mitral repair.

Methods

Surgical Preparation

The current study presents data from previously unreported interventions in our prior ovine experiment.¹⁴ The general surgical

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2 small Teflon-felt pledges thus creating a “double orifice” mitral valve (Figure 1B). The approximating suture or Alfieri stitch was placed approximately 5 mm from each leaflet edge and passed through 2 small holes on each side of the slit of the force transducer securing the transducer in place and approximating the leaflets. The force transducer was constructed of a slit copper ring, 5 mm in diameter and 0.4 mm thick. Technical specifications of the transducer have been previously described.17 Two pacing wires were placed on the right atrium and externalized.

After marker implantation, the heart was defibrillated, the animals weaned from cardiopulmonary bypass and transferred immediately to the experimental animal catheterization laboratory where they were studied intubated in open-chest, anesthetized condition. Simultaneous biplane videofluoroscopy, hemodynamic data recordings, and force transducer tension readings were measured before and after 2 experimental conditions: Rapid atrial pacing at 130 minutes1 (Apace) and bolus infusion of 1 gm of calcium chloride (Calcium).

Because of pacer noncapture, pacing data were available for only 5 animals, whereas all 8 animals had successful data acquisition during calcium infusion.

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. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

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-designed software18 to yield the 3-dimensional x,y,z coordinates for each of the radiopaque markers every 16.7 ms throughout the cardiac cycle. Force transducer tension, ascending aortic pressure, LV pressure, and ECG voltage signals were also digitized and recorded simultaneously.

Data Analysis
Two to 3 consecutive steady state beats before and after atrial pacing and calcium infusion were averaged and considered “Pre-Apace”, “Apace”, “Pre-calcium”, and “Calcium” data for each animal. During each cardiac cycle, end-systole (ES) was defined as the frame containing minimum LV volume; end-diastole (ED) was defined as the videofluoroscopic preceding the frame containing the peak LV volume. Instantaneous LV volume was computed from the LV markers as described previously.19 Stroke volume (SV) was calculated as the difference between end-diastolic LV volume (EDV) and end-systolic LV volume (ESV), whereas cardiac output was calculated as heart rate multiplied by stroke volume (CO=HR×SV).

Mitral Annular Dynamics
Mitral annular area (MAA) was computed from the 3-D coordinates of the 8 markers sutured to the mitral annulus using an annular centroid. The septal-lateral (SL) annular diameter was calculated as the distance in 3-D space between markers placed on the midanterior and midposterior mitral annulus.

Statistical Analysis
All data are reported as mean±1SD, unless otherwise shown. Hemodynamic and marker-derived data from 3 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 evaluation over a time period of 650 ms. The mean and SD for each variable at each sampling instant were then computed.
TABLE 1. Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Pre-Apace</th>
<th>Apace</th>
<th>Pre-Calcium</th>
<th>Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, min⁻¹</td>
<td>86±18</td>
<td>128±4*</td>
<td>86±18</td>
<td>87±19</td>
</tr>
<tr>
<td>LV dP/dt, mm Hg/s</td>
<td>1694±758</td>
<td>1645±795</td>
<td>1748±664</td>
<td>2562±511*</td>
</tr>
<tr>
<td>LV peak, mm Hg</td>
<td>110±11</td>
<td>102±12</td>
<td>116±14</td>
<td>132±23*</td>
</tr>
<tr>
<td>EDV, ml</td>
<td>176±32</td>
<td>151±31</td>
<td>162±31</td>
<td>161±35</td>
</tr>
<tr>
<td>ESV, ml</td>
<td>138±35</td>
<td>130±36</td>
<td>124±32</td>
<td>108±31*</td>
</tr>
<tr>
<td>SV, ml</td>
<td>38±14</td>
<td>21±6*</td>
<td>38±9</td>
<td>53±15*</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>3.1±0.9</td>
<td>2.6±0.9</td>
<td>3.3±0.9</td>
<td>4.5±1.1*</td>
</tr>
</tbody>
</table>

HR indicates heart rate; dP/dt, maximum positive rate of change of LV pressure; LVPmax, maximum LV pressure; EDV, LV end-diastolic volume; ESV, LV end-systolic volume; SV, stroke volume; CO, cardiac output.

*P<0.05 vs baseline by t test for paired comparisons.

Results

Hemodynamics

The mean animal weight was 68±5 kg, whereas average cardiopulmonary bypass and aortic cross-clamp times were 82±9 minutes and 61±7 minutes, respectively. Postmortem examination revealed proper seating of all implanted force transducers and correct position of inserted myocardial markers. Hemodynamic parameters before and after atrial pacing and calcium infusion are summarized in Table 1. Atrial pacing increased heart rate significantly with concurrent reduction in stroke volume resulting in unchanged cardiac output and no change in LV dP/dt. As expected, calcium infusion increased LV pressure, LV dP/dt, and stroke volume resulting in a 42% increase in cardiac output but no change in heart rate. Thus, isolated chronotropic and inotropic hemodynamic effects were achieved with atrial pacing and calcium infusion, respectively.

Force Transducer Tension

Force transducer tension, annular septal-lateral, and annular area throughout the cardiac cycle before and after rapid atrial pacing are illustrated in Figure 2. Before pacing, maximum transducer tension was observed in diastole and temporally coincided with peak SL diameter and annular area. Atrial pacing did not alter transducer tension and annular SL diameter, and area also did not change. As shown in Figure 3, baseline dynamics of leaflet approximating point tension and annular diameter and area before calcium infusion were similar to those observed before atrial pacing. With calcium infusion and significant increase in inotropic state and flow (Table 1), transducer tension did not change and annular dimensions were altered only slightly. Table 2 summarizes peak transducer tension, annular septal-lateral diameter, and annular area before and after the 2 experimental interventions. Maximum annular septal-lateral diameter decreased only by 0.6 mm with calcium infusion, whereas no significant change in maximum transducer tension was observed.

Discussion

The Alfieri edge-to-edge mitral repair represents an evolution of reparative techniques to offer the proven benefit of open surgical mitral valve repair to a wider clinical population. As the technique is based on approximating central edges of the mitral leaflets with sutures, the repair is usually reinforced with concomitant ring annuloplasty in standard and mini-invasive surgical approaches to ameliorate concerns about limited durability. New percutaneous interventional procedures simulating the edge-to-edge repair do not currently include such anular reduction, which may predispose the patient to premature repair failure if the leaflet approximating clip or suture pulls free. This concern is based on the surgical experience where omission of ring annuloplasty was associated with suboptimal results. It is plausible that excessive approximating stitch tension may adversely affect repair durability, yet neither the modes of repair failure nor the determinants of Alfieri stitch tension have yet been completely characterized. The current experimental observations revealed that stitch tension did not change with either inotropic or chronotropic stimulation whereas annular size changed only slightly. These data, combined with our prior results, suggest that annular geometry rather than hemodynamic factors predominates in determining the tension in the Alfieri stitch.

The current data are corroborated by our prior findings from the same sheep, where peak transducer tension occurred in diastole and coincided with peak annular SL diameter. Dobutamine infusion significantly augmented flow, heart rate, maximum transducer tension, and annular SL diameter and area before calcium infusion, respectively. Data were compared using Student t test for paired comparisons.
TABLE 2. Stitch Tension and Annular Geometry

<table>
<thead>
<tr>
<th></th>
<th>Pre-Apace</th>
<th>Apace</th>
<th>Pre-Calcium</th>
<th>Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{MAX}}$ N</td>
<td>0.27±0.17</td>
<td>0.34±0.20</td>
<td>0.29±0.11</td>
<td>0.32±0.10</td>
</tr>
<tr>
<td>$SL_{\text{MAX}}$ mm</td>
<td>31.7±3.1</td>
<td>32.1±3.3</td>
<td>29.9±3.3</td>
<td>29.3±3.5*</td>
</tr>
<tr>
<td>$MAA_{\text{MAX}}$ mm$^2$</td>
<td>991±92</td>
<td>986±136</td>
<td>892±134</td>
<td>857±130*</td>
</tr>
</tbody>
</table>

$I_{\text{MAX}}$ indicates maximum transducer tension; $SL_{\text{MAX}}$, maximum annular septal-lateral diameter; $MAA_{\text{MAX}}$, maximum mitral annular area.

*P<0.05 vs baseline by t test for paired comparisons.

decreased anterior leaflet stress near the approximating suture.\(^2^4\) It is therefore reasonable to conjecture that addition of annuloplasty to an Alfieri stitch should reduce stitch tension and any subsequent rise in leaflet stress imposed by annular dilatation. Whether this would translate into improved clinical outcomes remains speculative.

Although current data favor annular geometry over hemodynamic conditions as the primary determinant of Alfieri stitch tension, the effect of flow and transmural gradients cannot be ignored. A recent elegant in vitro study\(^1^5\) found peak approximating suture tension to be bimodally distributed during the cardiac cycle with the diastolic component predominating under normal annular geometry, supporting our results. With annular dilatation, on the other hand, systolic tension became predominant and diastolic tension varied inversely with annular size. This discordance with our current results may lie in the differences in transducer positioning, species differences (porcine versus ovine), in vitro versus in vivo conditions, annular diameter ratio (commissure-commissure to septal-lateral), or magnitude of 4-D perturbations in papillary muscle positions and shape of the mitral annulus. Mitral annular area and septal-lateral annular size in conjunction with mitral flow rate and transmural pressure, however, were independent predictors of systolic force transducer tension. Annular septal-lateral dilatation of 20% in this in vitro model significantly increased transducer tension and mitral regurgitation supporting the notion that the edge-to-edge repair should be performed along with some type of reducing annuloplasty.

Whether the results of our study can be extrapolated to the clinical arena remains to be demonstrated, although a recent phase I trial of percutaneous Alfieri edge-to-edge repair offers some insight.\(^1^1\) In this multicenter study, among the 24 pts who had a percutaneous Alfieri clip placed, 3 had clip detachments and another 3 developed recurrent 3+ MR after initial reduction of mitral insufficiency.\(^1^1\) It is difficult to speculate whether the modes of repair failure and recurrent MR were directly related to excessive stitch tension, but at the same time it is reasonable to conjecture that in patients discharged with intact repairs and no mitral regurgitation without annular rings high stitch tension attributable to annular dilatation could be a contributing factor. Although the measured Alfieri stitch tension in the current study appears small (range 0.25 to 0.35 N), it is consistent with computational values reported in the literature\(^2^3\) and in vivo measurements of tension in the first-order chordae tendineae during acute LV ischemia and mitral regurgitation.\(^2^5\) Therefore, we believe these tension values are clinically relevant during the cardiac cycle, especially over the long-term. Potentially a second percutaneous annuloplasty device\(^2^6\) could be added to the leaflet clip, akin to surgical practice, to reduce annular SL diameter and size, suture tension, and possibly improve repair durability, but we need to learn more about how interventional edge-to-edge repairs fail. The results of the current study argue for using an annular reducing procedure in conjunction with the Alfieri repair as annular size appears to be the chief determinant of stitch tension which could increase with progressive dilatation of an unsupported annulus. A direct causal link between these biomechanical find-
ings and clinical pathophysiology, however, remains to be established.

Limitations
The major limitations of this study are inherent to the animal model. Our tension measurements were obtained in sheep which were anesthetized and studied in open-chest conditions shortly after cardiopulmonary bypass. The surgical procedure necessitated implantation of small metallic markers around the mitral annulus which could theoretically affect valvular function. Echocardiographic studies, however, indicate that the markers do not interfere with mitral annular or leaflet motion as they are very small (aggregate mass = 20±6 mg). However, the force transducer, although small, is considerably larger than the implanted markers and could potentially distort leaflet geometry. Our previous experiments with dobutamine revealed that leaflet approximation with the force transducer permits normal annular motion and hence there is no “girdling” effect of leaflet approximation. Furthermore, leaflet edge displacement from the annular plane near each commissure at end-systole was found to be similar in control animals and those who had undergone leaflet approximation with the miniature force transducer. Therefore, a significant effect of the transducer on leaflet geometry, though feasible, is probably unlikely. Although annular size affects Alfieri stitch tension, and annular dilatation, especially in the septal-lateral dimension, increases suture tension, it is yet not known what effect increased suture tension has on the durability of the edge-to-edge repair. The current study investigated Alfieri stitch tension with approximation of the central edges of both leaflets; whether the current findings are applicable when an “asymmetric” double orifice repair is performed (ie, suture placed toward either commissure) is not known. Lastly, although neither baseline nor peak tension changed with the hemodynamic interventions used, it is possible that tension-time integral across the cardiac cycle could uncover subtle differences. We, however, did not explore this possibility, as we believe that peak tension would most likely be related to the clinical durability of the procedure and therefore the most pertinent parameter to examine and compare.

Differences between human and ovine mitral anatomy must also be considered in extrapolating current data to the clinical arena. In particular, leaflet occlusion area relative to the mitral orifice is smaller in sheep than in humans and annular dilatation may exhaust this maximal coaptation area in an ovine heart, but this may not be true in human hearts. Sheep have a less well defined posterior annulus than human and more atrial tissue above and below the line of leaflet insertion, but mitral annular dynamics are similar in both sheep and human hearts. Despite the limitations inherent in this particular experimental preparation, reliable models of cardiac pathophysiology have been established in ovine models. In the current study we used healthy animals with normal mitral valves, which is a departure from the clinical scenario of severe mitral regurgitation that is often associated with LV chamber enlargement, annular dilatation, and leaflet pathology.

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Disclosures
None.

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