Quantification and localization of mitral valve tenting in ischemic mitral regurgitation using real-time three-dimensional echocardiography

Liam Ryan, Benjamin Jackson, Landi Parish, Hiroaki Sakamoto, Theodore Plappert, Martin St. John Sutton, Joseph Gorman III, Robert Gorman

Abstract

Objective: Ischemic mitral regurgitation (IMR) results from a variable combination of annular dilatation and remodeling of the subvalvular apparatus. Current surgical techniques effectively treat annular dilatation, but methods for addressing subvalvular remodeling have not been standardized. An effective technique for determining the extent of subvalvular remodeling could improve surgical results by identifying patients who are unlikely to benefit from annuloplasty alone. Methods: A well-characterized ovine model of IMR was employed. Real-time three-dimensional echocardiography was performed on each animal at baseline, immediately after infarction and 8 weeks after infarction. Intercommissural width and mitral annular area were calculated for each subject at each time point. Mitral valve tenting area and height were calculated at discrete intervals along the entire intercommissural axis. The location at which maximal tenting area and height occurred was recorded. Mitral valve tenting volume was calculated by summation. Results: Both immediate and long-term increases were observed in mean intercommissural width and mitral annular area (from 33.2 to 36.3 to 39.7 mm and from 740 to 810 to 1020 mm², respectively). Both immediate and long-term increases were observed in maximum mitral valve tenting area and height (from 38.5 to 50.6 to 112.1 mm² and from 3.9 to 4.7 to 10.1 mm, respectively). Mitral valve tenting area and height at the mid-point of the intercommissural axis did not change significantly during the observation period. The position along the intercommissural axis at which maximal mitral valve tenting area and height occurred shifted progressively toward the anterior commissure (from 51.8% to 45.1% to 38.9% and from 52.9% to 45.1% to 37.8%). Both immediate and long-term increases were observed in mitral valve tenting volume (from 474.0 to 622.1 to 1483.5 mm³). Conclusions: We have described a technique that utilizes real-time three-dimensional echocardiography to perform a comprehensive assessment of leaflet tethering on the entire mitral valve. Our methodology is not influenced by viewing plane selection, regional tenting asymmetry, or annular dilatation and, therefore, represents a potentially useful surrogate measure of subvalvular remodeling.

Keywords: Mitral valve; Echocardiography; Surgery; Structure

1. Introduction

Ischemic mitral regurgitation (IMR) is mitral valve insufficiency that is caused by infarction induced ventricular remodeling [1]. The presence of even mild degrees of IMR is associated with significantly reduced survival rates [2,3]. These data have resulted in an increasingly aggressive surgical approach to IMR [4].

During the past decade, laboratory and clinical studies, using several different imaging modalities including sonomicrometry [5], marker tagged fluoroscopy [6], echocardiography [7], and MRI [8], have helped to elucidate the mechanisms that underlie IMR. These studies have demonstrated definitively that the two key anatomic elements that contribute to the development of IMR are annular dilatation and disruption of the dynamic anatomic relationship between the papillary muscles and the annulus. This remodeling of the subvalvular apparatus is manifest as tethering of the leaflets into the left ventricular cavity during systole. The extent to which each of these two parameters contributes to valvular incompetence varies substantially between individual patients [9].

While annular dilatation is readily quantified by standard two-dimensional echocardiographic techniques, methods for quantifying leaflet tethering have not been standardized. Descriptive geometric parameters based on single plane measurements made from two-dimensional echocardiographic studies, such as tenting height and area, have been proposed [9]. These measurements may be inaccurate due to...
the high variability of scanning planes and regional variation in mitral annular shape. Recent advances in three-dimensional echocardiography have led some authors to propose leaflet tenting volume as an indicator of subvalvular remodeling [10,11]. Tenting volume is, however, influenced by annular size and, therefore, is not a reliable, independent indicator of subvalvular remodeling.

In order to most accurately quantify the degree of mitral leaflet tethering in subjects with IMR, it is necessary to apply a three-dimensional interrogation of the entire valve which is independent of plane selection, regional tenting asymmetry, and annular dilatation. We have developed a unique methodology for using real-time three-dimensional echocardiography (rt-3DE) to quantitatively assess mitral leaflet tethering at discrete points along the intercommissural axis of the mitral valve in an established ovine model of IMR.

2. Materials and methods

2.1. Surgical protocol

The study protocol was reviewed and approved by the University of Pennsylvania School of Medicine Institutional Review Board. In compliance with guidelines for humane care (National Institutes of Health Publication No. 85-23, revised 1996), five male Dorsett hybrid sheep were pretreated with buprenorphine (2 mcg/kg) and then induced with sodium thiopental (10—15 mg/kg IV), intubated and anesthetized with isofluorane (1.5—2.0%) and oxygen (Narkomed, North American Drager). All animals received glycopyrrolate (0.02 mg/kg IV) and cefazolin (1.0 g IV). The electrocardiogram, arterial blood pressure, and pulmonary artery pressure were monitored throughout the procedure. A left thoracotomy was performed and baseline data were acquired. A posterobasal myocardial infarction was then performed by ligating all branches of circumflex coronary artery between the anterior and posterior mitral annular points in a given plane (panels A and B), while mitral valve tenting height (MVTh) was defined as the orthogonal distance between this septolaterally oriented line and the leaflet tips (panels C and D). Both parameters were calculated at known intervals, $\Delta c$, along the entire length of the intercommissural axis.

2.2. Data collection protocol

Real-time three-dimensional echocardiography was performed immediately prior to, 1 h after and 8 weeks after myocardial infarction in all subjects. Full-volume data sets were acquired by a single operator using a Sonos 7500 (Philips Medical Systems, Andover, Massachusetts) platform equipped with a 2—4 MHz X4 handheld transducer. The degree of mitral regurgitation was determined quantitatively by assessing the area of the regurgitant jet as a percentage of left atrial area. The following grading was used: grade $1 < 20\%$; grade $2 = 20—40\%$; grade $3 = 40—60\%$; and grade $4 > 60\%$ [12].

2.3. Image analysis

Full-volume data sets were first exported to a QLab 3D Advanced Quantification Software (Philips Medical Systems, Andover, Massachusetts) workstation for calculation of LV cavity volumes. For each data set, endocardial contours were manually traced in both end diastolic and end systolic frames, which were selected by visual inspection. The endocardial contours of the remaining frames were traced in sequence by means of automated contour detection. Left ventricular end diastolic volume (LVEDV) and left ventricular end systolic volume (LVESV) were derived from the resultant global time-volume curve for each data set. The corresponding ejection fraction (EF) was calculated in the standard fashion.

Each full-volume data set was then exported to a separate Tomtec Cardioview (Tomtec Imaging Systems, Munich, Germany) workstation for quantitative analysis. All calculations were performed at end-systole. Each volume was centered in such a fashion that the short axis intersected the mitral annulus at its aortic and mid-posterior peaks. The volume was then rotated and translated so that the paramedian long axis bisected the anterior and posterior mitral commissures (thus effectively defining the intercommissural axis) and the septolateral long axis bisected the mitral valve orifice. As illustrated in Fig. 1, mitral valve tenting area (MVTa) was defined as the area enclosed by the mitral leaflets and a septolaterally oriented line connecting juxtaposed anterior and posterior mitral annular points in a given plane (panels A and B), while mitral valve tenting height (MVTh) was defined as the orthogonal distance between this septolaterally oriented line and the leaflet tips (panels C and D). Both parameters were calculated at known intervals, $\Delta c$, along the entire length of the intercommissural axis.
Mitral valve geometric parameters as calculated for each measurement interval are presented as mean ± standard deviation. Subsequent to a two-tailed, paired *t*-tests were used. For all comparisons, *P* ≤ 0.05 was considered significant. The following geometric end point variables were analyzed: CW, MAA, MVThmax, PosMVThmax, MVThmid-CW, MVThmax, PosMVThmid-CW, MVThmax, MVTa mid-CW, MVTh, LVEDV, LVESV, and EF.

Table 1
Mitral valve geometric parameters as calculated for each measurement interval are presented as mean ± standard deviation

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 h after infarction</th>
<th>8 weeks after infarction</th>
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<tbody>
<tr>
<td>CW (mm)</td>
<td>32.2 ± 1.7</td>
<td>36.3 ± 2.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>39.7 ± 3.1&lt;sup&gt;b,c&lt;/sup&gt;</td>
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<tr>
<td>MAA (mm²)</td>
<td>740 ± 37</td>
<td>810 ± 46&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1020 ± 250&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>MVThmid-CW (mm²)</td>
<td>32.0 ± 8.2</td>
<td>33.6 ± 17.4</td>
<td>68.0 ± 38.2</td>
</tr>
<tr>
<td>MVThmax (mm²)</td>
<td>38.5 ± 9.0</td>
<td>50.6 ± 10.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>112.1 ± 15.1&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>PosMVThmax (%)</td>
<td>51.8 ± 3.4</td>
<td>45.1 ± 6.8</td>
<td>38.9 ± 7.5&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>MVThmid-CW (mm)</td>
<td>3.5 ± 1.0</td>
<td>3.3 ± 1.1</td>
<td>3.3 ± 1.91</td>
</tr>
<tr>
<td>MVThmax (mm)</td>
<td>3.9 ± 0.8</td>
<td>4.7 ± 0.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.1 ± 1.6&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>PosMVThmid (%)</td>
<td>52.9 ± 5.2</td>
<td>45.1 ± 6.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>37.8 ± 5.9&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>MVTv (mm³)</td>
<td>474.0 ± 120.4</td>
<td>622.1 ± 170.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1483.5 ± 416.8&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>40.7 ± 4.3</td>
<td>55.72 ± 10.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>68.4 ± 6.8&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>20.6 ± 5.7</td>
<td>34.4 ± 11.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>46.6 ± 7.8&lt;sup&gt;b,c&lt;/sup&gt;</td>
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<tr>
<td>EF (%)</td>
<td>49.9 ± 9.5</td>
<td>39.2 ± 10.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31.9 ± 6.8&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>MR grade</td>
<td>0—1+</td>
<td>2—3+</td>
<td>3+</td>
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<sup>a</sup> *P* < 0.05 when compared to baseline value.

<sup>b</sup> *P* < 0.05 when compared to baseline value.

<sup>c</sup> *P* < 0.05 when compared to the value obtained 1 h after infarction.

(Fig. 2). Intercommissural width (CW) was defined as the sum of these discrete intercommissural measurement intervals for a given data set. Mitral annular area (MAA) was defined as the area enclosed by a two-dimensional short axis projection of the marked annular points for a given subject. Mitral valve tenting volume (MVTv), which was defined as the sum of the incremental regional volumes MVTa × Δcn, was calculated as follows:

\[
MVTv = \sum MVTa(n)\Delta cn + MVTa(n+1)\Delta cn+1 + \ldots
\]

For each data set, both MVTa and MVTh were plotted as a function of their intercommissural position. In order to allow for inter-subject comparison, intercommissural position was expressed as a percentage of the distance traveled between the anterior commissure and the posterior commissure, where 0% indicated the position of the anterior commissure and 100% indicated the position of the posterior commissure. The values of MVTa and MVTh at the mid-point of the intercommissural axis width (defined as MVThmid-CW and MVThmid-CW respectively) were recorded for each data set. The maximum segmental MVTa and MVTh (MVThmax) and their associated positions along the intercommissural axis (PosMVThmax and PosMVThmid-CW) were recorded for each subject.

### 2.4. Statistical analyses

For comparison of echocardiographic parameters between time points, two-tailed, paired *t*-tests were used. For all comparisons, *P* ≤ 0.05 was considered significant. The following geometric end point variables were analyzed: CW, MAA, MVThmax, PosMVThmax, MVThmid-CW, MVThmax, PosMVThmid-CW, MVThmid-CW, MVTv, LVEDV, LVESV, and EF.

### 3. Results

None of the animals had significant MR at baseline. All animals developed significant early (1+ to 2+) and late (3+) IMR. Echocardiographic data are summarized in Table 1. All values are expressed as mean ± standard deviation. Substantial left ventricular remodeling occurred in all animals over the 8-week follow-up interval. LVEDV increased from 40.7 ± 4.3 ml at baseline to 55.7 ± 10.6 ml at 1 h after infarction and to 68.4 ± 6.8 ml at 8 weeks after infarction. LVESD increased from 20.6 ± 5.7 ml at baseline to 34.4 ± 11.9 ml and 46.7 ± 7.8 ml, respectively, over the same intervals, while EF decreased from 49.9 ± 9.5% to 39.2 ± 10.7% and 31.9 ± 6.8%, respectively.

All animals developed significant annular dilatation as the ventricle remodeled. CW increased from 33.2 ± 1.7 mm at baseline to 36.3 ± 2.4 mm at 1 h after infarction and 39.7 ± 3.1 mm at 8 weeks after infarction. MAA increased from 740 ± 37 mm² at baseline to 810 ± 46 mm² at 1 h after infarction and 1020 ± 250 mm² at 8 weeks after infarction. MVThmid-CW and MVThmid-CW both increased during remodeling—from 32.0 to 33.6 to 68.0 mm² and from 3.5 to 3.3 to 5.3 mm², respectively.

### References

Fig. 3. Mitral valve tenting area (MVTa) as a function of intercommissural position (expressed as a percentage of the distance traveled from the anterior commissure) is shown for each of the five subjects. Both a small increase in maximal tenting area and a bias toward the anterior commissure are apparent at the post-MI time point. Both of these geometric changes are more pronounced at the 8-week follow-up time point.

Fig. 4. Mitral valve tenting height (MVTh) as a function of intercommissural position is shown for each of the five subjects. Both a small increase in maximal tenting height and a bias toward the anterior commissure are apparent at the post-MI time point. Both of these geometric changes are more pronounced at the 8-week follow-up time point.
Mitral leaflet tethering was confirmed by increases in MV$T_{a\text{max}}$ from 38.5 ± 9.0 to 50.6 ± 10.1 and 112.1 ± 15.1 mm$^2$, respectively, and MV$T_{h\text{max}}$ from 3.9 ± 0.8 to 4.7 ± 0.9 and 10.1 ± 1.6 mm, respectively. MV$T_h$ also increased from 474.0 ± 120.4 mm$^3$ at baseline to 622.1 ± 170.2 mm$^3$ at 1 h after infarction and to 1483.5 ± 416.8 mm$^3$ at 8 weeks after infarction. Interestingly, the position of maximum tenting area and height was shifted from the center of intercommissural axis toward the anterior commissure as remodeling progressed: PosMV$T_{a\text{max}}$ decreased from 51.8 ± 3.4% of the distance traveled from the anterior commissure to the posterior commissure to 45.1 ± 6.8% and to 38.9 ± 7.5% at 1 h and 8 weeks after infarction respectively. Similarly, PosMV$T_{h\text{max}}$ decreased from 52.9 ± 5.2% to 45.1 ± 6.8% and 37.8 ± 5.9%, respectively. The statistical significance of these changes and other measured parameters are presented in Table 1.

Fig. 5. Average MV$T_a$ ± standard deviation for the cohort is plotted as a function of intercommissural position. Both a small increase in maximal tenting area and a bias toward the anterior commissure remain evident following MI when the five data sets are merged. Again, these geometric changes are more pronounced at the 8-week follow-up time point.

Mitral valve tenting area and height are plotted as functions of their intercommissural position individually for each of the five subjects in Figs. 3 and 4, respectively. Mean mitral valve tenting area and height for the entire cohort are plotted as functions of their intercommissural position in Figs. 5 and 6, respectively.

4. Discussion

We have described a technique that utilizes real-time three-dimensional echocardiography to perform a comprehensive assessment of leaflet tethering on the entire mitral valve. Our methodology is not influenced by viewing plane selection, regional tenting asymmetry, or annular dilatation and, therefore, represents a potentially useful surrogate measure of subvalvular remodeling.

Interestingly, our data demonstrate that leaflet tethering develops asymmetrically in this model as the area of maximal tenting shifts from the center of the valve toward the anterior commissure during remodeling. This pronounced asymmetry confirms that single-plane-based indexes of leaflet tenting determined by means of standard two-dimensional echocardiographic techniques, such as MV$T_a$ and MV$T_h$, are unreliable for effectively and reproducibly quantifying the degree of leaflet tethering.

The anterior shifting of the maximum tenting leaflet location seems counterintuitive, given the fact that the infarct used in this experiment was located in the posterolateral region of the LV, directly under the posterior commissure. Previous studies in our laboratory help to explain this interesting finding. IMR in this model, as in humans, develops concomitantly with global LV dilation which influences the relationship between both papillary muscles and their relationship with the annulus. Using sonomicrometry to study this model, we have documented substantial increases in the distance between the tip of the anterior papillary muscle and the anterior as well as the posterior commissures [5]; these changes are consistent with the leaflet tenting profile demonstrated in this experiment. Whether this tenting pattern occurs clinically remains to be determined, but given the fidelity of the ovine model to the human disease, we believe that it is highly likely that similar changes will be manifest, at least in a subset of patients with IMR. The potential importance of the anterior papillary muscle to leaflet tenting in IMR has implications for evolving surgical approaches that are solely focused on re-establishing posterior papillary–annular geometry [13,14].

Although mitral valve repair has gained wide acceptance as the treatment of choice for IMR [4], recent data indicate that this technique is associated with a surprisingly high incidence of both early and late recurrences of mitral regurgitation [15,16]. This lack of durability may be partially responsible for the difficulty in demonstrating a survival advantage for IMR patients treated with surgical valve repair compared to medically treated patients or patients having only surgical revascularization [17,18]. Our technique for quantifying and localizing remodeling induced mitral leaflet tethering has potential for improving surgical results by optimizing preoperative planning for patients with IMR based...
on the relative degree to which leaflet tethering and annular dilatation contribute to valvular incompetence (i.e., repair vs. replacement).

The extent of total leaflet tethering is potentially a valuable surrogate measure of subvalvular remodeling. We propose that our comprehensive technique for measuring leaflet tenting is a reliable, quantitative measure of whole- valve tethering which accurately reflects the contribution of subvalvular remodeling to the extent of IMR. Longitudinal clinical follow-up of patients having surgery for IMR will be required to determine the extent of leaflet tethering that is associated with durable relief from IMR after ring annuloplasty.

As discussed above, the data presented here and the data we have previously published [5, 19] demonstrate that the geometric remodeling that occurs in conjunction with IMR is not limited to the posterior annulus, the posteromedial papillary muscles, or the posterior commissure. Significant changes involving the anterior annulus, the anterolateral papillary muscles, and the anterior commissure have been observed as well. These data strongly suggest that IMR, even in the case of experimental, highly reproducible infarctions limited exclusively to the posterior wall of the left ventricle, such as those utilized in this study, involves global ventricular remodeling. Therefore, the generalized application of repair strategies that focus on normalizing isolated subvalvular geometric relationships would seem ill advised. However, individualized procedures designed to address patient-specific valve tethering patterns that are characterized using meticulous three-dimensional reconstruction algorithms similar to those described in this report may improve the durability and efficacy of procedures for IMR.

Our methodology allows the magnitude of leaflet tethering across the entire surface of the mitral valve to be determined and provides a surrogate measure of remodeling-induced changes in the geometry of the subvalvular apparatus. This technique may effectively allow surgeons to stratify patients with IMR into those likely to sustain long-term clinical benefits from restorative procedures such as mitral annuloplasty and those less likely to sustain such benefits. In the future, the ideal surgical repair for ischemic mitral regurgitation will likely be individually tailored after the durability and efficacy of procedures for IMR.

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References