Quantitative measurement of mitral valve coaptation in functional mitral regurgitation: In vivo experimental study by real-time three-dimensional echocardiography

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Summary
Background: The degree of mitral valve (MV) coaptation should be an important parameter in the assessment of functional mitral regurgitation (MR). This study aimed to quantify the degree of MV coaptation in experimental models of functional MR caused by acute left ventricular (LV) pressure overload, using real-time three-dimensional (3D) echocardiography.

Methods and results: Using canine models, LV pressure overload was induced by staged ascending aortic banding. Echocardiographic examinations were performed before and during the aortic banding. By using a novel software system for 3D quantification (REALVIEW®), the annulus and leaflet were traced manually both at the onset of MV closure and at the maximum MV closure. The coaptation index was calculated by the following formula: [((3D tenting surface area at the onset of MV closure - 3D tenting surface area at the maximum MV closure) / 3D tenting surface area at the onset of MV closure)] × 100.

MR area gradually increased with the decrease in coaptation index during progressively exacerbated aortic banding. MR area was significantly correlated with the coaptation index. A coaptation index <12 had a high sensitivity and specificity in the presence of significant MR.
Introduction

Functional mitral regurgitation (MR) is an important complication that adversely affects the prognosis in patients with ventricular dysfunction [1—10]. In patients with functional MR, restriction of leaflet closure occurs mainly as a result of: (1) dilation of the mitral annulus, and (2) papillary muscle displacement due to left ventricular (LV) dilatation.

The degree of mitral valve (MV) leaflet coaptation should be considered as an important parameter in the assessment of functional MR. However, there have been no imaging modalities to evaluate the actual degree of coaptation, so that tenting area [11,12], tenting depth [13], or tenting length [14] has been used as a surrogate for the coaptation in the clinical setting. The degree of MV leaflet coaptation should be an important parameter in the assessment of mitral apparatus geometry before and after MV repair surgery for functional MR.

Recently, we have successfully demonstrated the three-dimensional (3D) quantitation of mitral apparatus geometry using a custom software system with 3D echocardiography [15] in human beings, and our previous reports clearly showed mitral leaflets bulging toward the LV in functional MR with LV dysfunction [5,16—20]. By using the 3D quantification system, we have demonstrated a decrease in MV coaptation index in patients with dilated cardiomyopathy [5].

Therefore, we sought to evaluate the relationship between the quantified degree of MV coaptation and the occurrence of functional MR by using the 3D analysis system with real-time 3D echocardiography. To produce dynamic changes in the MV apparatus geometry, we used aortic banding canine models with acute LV pressure overload in the present study.

Methods

Experimental model

Three adult mongrel dogs (20—28 kg) anesthetized with ketamine hydrochloride (10 mg/kg i.m.) and droperidol (0.5 mg/kg i.v.) were ventilated. Two 5F pigtail catheters were inserted into the bilateral femoral arteries and advanced to monitor LV pressure and descending aortic pressure simultaneously.

Thoracotomy was made through the midline and a rubber tube for aortic banding was placed around the ascending aorta [21]. Tubing was wrung slowly to increase the LV-aorta pressure gradient up to 60, 90, and 120 mmHg. This process was repeated three times in each dog. Mitral complex geometry and the degree of MR were measured by acquiring two-dimensional (2D) and real-time 3D echocardiograms in each condition. After acquiring the image, the rubber band was released to diminish the LV pressure.

Echocardiographic protocol

All the echocardiographic examinations were performed by using ultrasound equipments (iE33®, Philips Medical Systems, Bothell, WA, USA) with S3 probe for 2D images and X3-1 probe for real-time 3D images [16—20].

2D echocardiographic study

Volumetric image acquisition

Epicardial volumetric images (full-volume mode) in apical view were obtained using a real-time 3D echocardiographic system in all the subjects. The volumetric frame rate was 22 frames/s, with an imaging depth of 9 cm. Before acquiring the full volume image, we carefully adjusted. All the volumetric transducers were positioned at the apex in a biplane mode. All the volumetric
images were digitally stored on compact disk and transferred into a personal computer for offline analysis.

**Quantification of MV geometry by 3D echocardiography**

Based on previous studies \[5,16–20\], 3D volumetric images were radially cropped 10 degrees apart by utilizing a custom software system (REALVIEW®, YD, Osaka, Japan). The mitral annulus was then manually marked and the MV leaflet was semi-automatically traced in mid systole.

3D morphology of mitral complex was reconstructed, and annular area, tenting volume, tenting length, and 3D tenting surface area were quantified. Tenting volume was calculated as the volume enclosed between the annular plane and mitral leaflets. Tenting length was defined as the distance from the annular plane to the most tethered leaflet site in the 3D data. 3D tenting surface area was calculated from the 3D dataset as well. 3D tenting surface area does not include coapted leaflet area in this study \[5,16–20\].

To evaluate the degree of leaflet coaptation, 3D reconstruction was done in selected 2 frames; (1) at the onset of MV closure and (2) at the maximum MV closure. When the MV closes, the tips of the leaflets touch first, and then, as the leaflets coapt, the tenting surface area decreases. Therefore, changes in the tenting surface area in these two frames reflect the degree of MV coaptation \[5\].

The coaptation index was calculated by the following formula: \[
\frac{(3D \text{ tenting surface area at the onset of MV closure}-3D \text{ tenting surface area at the maximum MV closure})}{3D \text{ tenting surface area at the onset of MV closure}} \times 100
\] (Fig. 1) \[5\].

![Figure 1](image_url) Mitral valve (MV) apparatus geometry at the onset of mitral leaflet closure and the timing of maximum closure of the mitral leaflet. To evaluate the degree of leaflet coaptation, three-dimensional reconstruction was done in selected 2 frames: (1) at the onset of MV closure and (2) at the maximum MV closure. When the MV closes, the tips of the leaflets touch first, and then, as the leaflets coapt, the tenting surface area decreases. Hence, changes in the tenting surface area in these two frames reflect the degree of MV coaptation. A, anterior; P, posterior; M, medial; L, lateral.
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Quantification of the LA and LV volumes by 3D echocardiography
LA volume and LV volume were quantified by the custom software system (Q-Lab®, Philips Medical Systems) in mid systole.

Statistical analysis
Results are expressed as the mean value ± SD. Group comparisons were made using the Student t-test for continuous variables. A p value of <0.05 was considered significant. Receiver-operating curve analysis was used with the calculation of the area under curves. A threshold value was determined for the most significant variables to obtain better separation power against the degree of MR.

Results
Fig. 2 shows 2D color Doppler images and reconstructed 3D images of MV apparatus in each stage. Changes in each parameter during aortic banding are summarized in Table 1.

Functional MR and MV apparatus geometry
Functional MR appeared in the course of incremental aortic banding. During acute aortic banding, the

![Figure 2](image)

**Figure 2** Two-dimensional color Doppler images and reconstructed three-dimensional (3D) images of the mitral valve apparatus during aortic banding. Functional mitral regurgitation appeared in the course of incremental aortic banding (upper). Reconstructed 3D images revealed annular dilation with leaflet tenting (coded by the yellow and red area) during aortic banding (lower). LA, left atrial; LV, left ventricular.

![Figure 3](image)

**Figure 3** Relationship between the degree of MR and the coaptation index measured by three-dimensional echocardiography. MR area/LA area was significantly correlated with the coaptation index \( r = 0.852, \ p < 0.0001 \). Functional MR was not significant until the coaptation index reached to a certain threshold. Once the coaptation index became smaller than the threshold, linear progression of MR was seen along with the decrease in coaptation index. A coaptation index < 12 had a sensitivity of 77% and specificity of 90% in the presence of significant MR (MR area/LA area < 20%). MR, mitral regurgitation; LA, left atrial.
Table 1  Changes in echocardiographic parameters during LV pressure overload.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>60mmHg</th>
<th>90mmHg</th>
<th>120mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>107 ± 11</td>
<td>124 ± 18</td>
<td>133 ± 25</td>
<td>150 ± 20</td>
</tr>
<tr>
<td>LV BP, systole (mmHg)</td>
<td>112 ± 21</td>
<td>155 ± 10</td>
<td>184 ± 7*</td>
<td>207 ± 18*</td>
</tr>
<tr>
<td>Ao BP, systole (mmHg)</td>
<td>102 ± 20</td>
<td>113 ± 20</td>
<td>123 ± 40</td>
<td>127 ± 57</td>
</tr>
<tr>
<td>LA volume (ml)</td>
<td>10.2 ± 1.7</td>
<td>11.5 ± 2.2</td>
<td>12.7 ± 2.1*</td>
<td>13.5 ± 2.8*</td>
</tr>
<tr>
<td>LV volume (mid-systolic) (ml)</td>
<td>11.1 ± 3.3</td>
<td>12.6 ± 3.6</td>
<td>13.7 ± 2.5*</td>
<td>18.2 ± 5.2*</td>
</tr>
<tr>
<td>LV long-axis dimension (mm)</td>
<td>39.1 ± 2.9</td>
<td>39.7 ± 0.8</td>
<td>41.7 ± 2.9</td>
<td>42.0 ± 2.0</td>
</tr>
<tr>
<td>LV short-axis dimension (mm)</td>
<td>21.3 ± 3.8</td>
<td>24.4 ± 4.0</td>
<td>27.0 ± 3.8*</td>
<td>32.2 ± 3.3*</td>
</tr>
<tr>
<td>Sphericity index</td>
<td>0.55 ± 0.10</td>
<td>0.61 ± 0.10</td>
<td>0.65 ± 0.08</td>
<td>0.77 ± 0.07*</td>
</tr>
<tr>
<td>Annular area (mm²)</td>
<td>5.0 ± 1.1</td>
<td>5.9 ± 1.3</td>
<td>6.3 ± 0.9*</td>
<td>6.8 ± 0.9*</td>
</tr>
<tr>
<td>Tenting volume (ml)</td>
<td>0.4 ± 0.2</td>
<td>0.6 ± 0.2*</td>
<td>0.6 ± 0.4</td>
<td>0.6 ± 0.3*</td>
</tr>
<tr>
<td>Tenting length (mm)</td>
<td>2.2 ± 0.6</td>
<td>2.7 ± 0.9</td>
<td>2.7 ± 0.7</td>
<td>2.7 ± 1.2</td>
</tr>
<tr>
<td>MR area/LA area (%)</td>
<td>3.3 ± 3.0</td>
<td>8.8 ± 9.4*</td>
<td>24.1 ± 19.2*</td>
<td>60.4 ± 24.7*</td>
</tr>
</tbody>
</table>

LA, left atrial; LV, left ventricular; MR, mitral regurgitation Ao, aorta; BP, blood pressure.

†p < 0.05 vs. baseline.
* p < 0.01 vs. baseline.

mitral annular area was gradually increased. Tenting length did not significantly change in this study. Tenting volume was slightly increased during aortic banding, but the change was not statistically significant.

MR area/LA area was significantly correlated \( (r = 0.852, p < 0.0001) \) with the coaptation index during aortic banding (Fig. 3). A coaptation index <12 had a sensitivity of 77% and specificity of 90% in the presence of significant MR.

MR area/LA area was significantly correlated \( (r = 0.385, p < 0.05) \) with the annular area during aortic banding (Fig. 4). However, the MR area/LA area had no correlation with the tenting length and tenting volume during aortic banding (Fig. 5A and B).

Changes in the hemodynamics, LA, and LV volume

Hemodynamic alterations during aortic banding are shown in Table 1. Immediately after LV-aorta pressure gradient up to 120 mmHg, LV systolic pressure increased significantly \((112 ± 21 \text{ to } 207 ± 18 \text{ mmHg}, p = 0.0043)\). However, systolic aortic pressure and heart rate did not increase significantly during aortic banding.

MR area/LA area was significantly increased as LA and LV volume increased in mid systole. MR area/LA area was significantly correlated with the LA and LV volume (Fig. 6A and B). The long-axis dimension of the LV did not increase during aortic banding while the short-axis dimension significantly increased. The sphericity index was increased from 0.55 ± 0.10 to 0.77 ± 0.07 \((p < 0.01)\) by acute LV pressure overload (Table 1).

Discussion

In the present study, we have investigated the relationship between the mitral apparatus geometry and the occurrence of functional MR in acute LV pressure overload, with the use of 3D quantitation system for real-time 3D echocardiography. Functional MR occurred during acute aortic banding along with the loss of coaptation and MV coaptation index <12 had high sensitiv-
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Dilation of the mitral annulus, papillary muscle displacement due to LV dilatation, and apical shift of the leaflets (so-called tenting phenomenon) are the characteristic findings in functional MR [1—6,14,16,17,20,24—27]. These geometric changes in the MV apparatus commonly occur in patients with LV remodeling, such as ischemic heart disease or dilated cardiomyopathy. Loss of coaptation occurs as a result of the annular dilation and/or leaflet tethering toward apex, and quantitative measurement of MV coaptation should be an important parameter in the assessment of the mechanism of functional MR.

This study was designed to quantitatively evaluate the relationship between the degree of coaptation and the occurrence of functional MR. The results have shown that functional MR increased along with LA and LV dilation derived by acute LV pressure overload. Dilatation of annulus and decrease of coaptation were the major findings in our canine model. MV tenting and tethering parameters were increased, but the changes were not significant. We assume that valve tenting and tethering parameters would significantly be changed in the myocardial dysfunction model, mimicking dilated cardiomyopathy or ischemic heart disease. In this study functional MR was not significant until the coaptation index reached a certain threshold. Once the coaptation index became smaller than the threshold, linear progression of MR was seen along with the decrease in coaptation index. This result would explain the dynamic changes in the degree of functional MR depending on clinical conditions, such as during the intensive treatment of congestive heart failure, or during exercise stress. Quantitation of the degree...
of MV coaptation can contribute in assessing the mechanisms of functional MR under various clinical conditions. Clinical trials are needed to assess whether these quantitative parameters obtained from real-time 3D echocardiography would contribute to evaluate further the mechanism of functional MR. Then these parameters could act as a guide in selecting the proper therapeutic strategy for each individual in the clinical setting.

Limitations

Firstly, the present study was designed to evaluate the relationship between MV morphological changes and occurrence of functional MR. Our animal model with functional MR was made by acute LV pressure overload, which was a different condition from chronic LV pressure overload or cardiomyopathies. Further evaluation of the MV geometry in various conditions, including animal studies and clinical studies are necessary.

Secondly, the frame rate of real-time 3D echocardiographic images is lower than that of conventional 2D echocardiography. Hence the number of conventional 3D frames during the cardiac cycle is relatively small in the canine models with a rapid heart rate. Therefore, the timing of 2D/3D measurements would not be exactly the same in each condition. There is a possibility that we missed the very beginning of the MV closure. In such cases, the calculated MV coaptation index does not precisely reflect the actual degree of coaptation. We have not validated the accuracy of the measurements compared with the actual length of the leaflets.

Thirdly, the method to quantify the severity of MR is a coarse way. Unfortunately, there was not enough time for other volumetric methods or regurgitant orifice area during acute aortic banding. Because accurate apical views were not easy to obtain from animal models, the LA was usually foreshortened in the apical 4-chamber view. This may affect the accuracy of measurements of, not only LA area but also MR jet area.

Conclusions

In acute LV pressure overload, functional MR appeared along with geometric changes in the mitral apparatus. The coaptation index calculated by using 3D echocardiography can be a useful parameter in the assessment of the mechanisms of functional MR.

Conflict of interest

All authors have no conflict of interest or financial disclosure regarding this manuscript.

References

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