Influence of Chronic Tethering of the Mitral Valve on Mitral Leaflet Size and Coaptation in Functional Mitral Regurgitation

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OBJECTIVES The purposes of this study were to examine whether tethering of the mitral leaflets affects coaptation in patients with functional mitral regurgitation (FMR) and to assess the interaction between the mitral coaptation and mitral regurgitation severity.

BACKGROUND Functional mitral regurgitation causes restriction of leaflet closure as a result of enhanced tethering of the mitral leaflets and papillary muscle (PM) displacement.

METHODS Three-dimensional transesophageal echocardiography was performed in 44 patients with FMR related to the bilateral PM displacement and in 56 controls. The distance between the tip of the anterior or posterior PM and the intervalvular fibrosa were measured as the lateral or medial tethering length (TL) in midsystole. To evaluate the degree of coaptation, coaptation length (CL) at medial, middle, and lateral sites of mitral valve and an estimate of coaptation area (CA) were measured.

RESULTS The FMR group showed the significantly decreased CA (1.3 ± 0.4 cm² vs. 1.6 ± 0.4 cm², p = 0.005) and CL (medial 3.2 ± 0.9 mm vs. 4.8 ± 0.6 mm, middle 3.8 ± 1.3 mm vs. 5.8 ± 0.7 mm, lateral 3.3 ± 0.9 mm vs. 4.8 ± 0.6 mm; all p < 0.0001) compared with the controls. Each CL correlated negatively and significantly with both medial and lateral TL (all p < 0.0001). Annular area (p = 0.004) was significantly smaller and leaflet-to-annular area ratio (p < 0.0001) was significantly larger in patients with nonsignificant FMR than in the patients with significant (moderate to severe) FMR. Significant correlations were found between effective regurgitant orifice area and CA or each CL (all p < 0.0001).

CONCLUSIONS Coaptation decreased significantly in patients with FMR. The CL at each region was related to PM displacement and the indexes of coaptation were associated with mitral regurgitation severity. (J Am Coll Cardiol Img 2012;5:337–45) © 2012 by the American College of Cardiology Foundation
Functional mitral regurgitation (FMR) typically occurs in patients with ischemic cardiomyopathy (ICM) and dilated cardiomyopathy (DCM) and is associated with excessive mortality (1–3). FMR causes restriction of leaflet closure as a result of dilation of the mitral annulus, enhanced tethering of the mitral valve (MV) leaflets, papillary muscles (PM) displacement, and reduced closing force of the leaflets without primary valve leaflet pathology (4–8).

Recently, it has been suggested that leaflets may be elongated in response to stress imposed by increased tethering (9). It has been shown that patients with mitral leaflet tethering caused by DCM or inferior myocardial infarction have larger mitral leaflet areas than the controls with normal heart measured by 3-dimensional (3D) echocardiography (10). Therefore, patients with insufficient adaptation to the tethered valve geometry could have incomplete leaflet closure and more mitral regurgitation (MR). However, there was a limitation in evaluating regional mitral leaflet coaptation, and little is known about the interaction between MR severity and indexes of the coaptation. The recent development of 3D transesophageal echocardiography (TEE) made it possible to provide excellent images of MV apparatus and accurate measurements of the mitral complex (11,12) Our aims were: 1) to examine whether chronic tethering of the mitral leaflets affects MV size, coaptation area, and regional coaptation length in patients with FMR; and 2) to assess the interaction between indexes of the mitral coaptation and MR severity.

**METHODS**

**Patient population.** Forty-four patients (age 68 ± 7 years, 38 men) with FMR related to bilateral PM displacement (n = 44; 18 with DCM, 26 with ICM) were recruited for 3D echocardiographic examination. In 26 patients with ICM, the infarct-related artery was the left anterior descending artery in 26 patients (100%), the right coronary artery in 22 patients (85%), and the left circumflex artery in 20 patients (77%). To clarify the determinants of MR, study patients were characterized as having significant (moderate or severe) MR, defined by the effective regurgitant orifice area (EROA) ≧0.2 cm² or nonsignificant MR if the EROA was <0.2 cm² based on recommendations by the American Society of Echocardiography (13). MR was quantified by the EROA calculated by either the proximal isovelocity surface area method or the quantitative pulse wave Doppler method using mitral and aortic stroke volumes (14). Fifty-six subjects (ages 67 ± 12 years, 31 men) who have no MR with normal left ventricular (LV) function and mitral apparatus were also examined as controls. Exclusion criteria were: 1) organic MV or subvalvular lesion (e.g., mitral leaflet prolapse or rheumatic disease); and 2) other cardiac diseases (e.g., pericardial, congenital, endocarditis, and aortic valve disease). The ethics committee of Kawasaki Medical School approved this study protocol.

**Conventional echocardiographic examination.** Two-dimensional transthoracic echocardiography was performed on patients in the left lateral decubitus position using a commercially available echocardiographic machine (iE33, Philips Medical Systems, Andover, Massachusetts) with a 5-MHz transducer. In the parasternal long-axis view, LV end-diastolic diameter, end-systolic diameter, and left atrial dimension were measured as reported previously. The LV end-diastolic volume, LV end-systolic volume, and LV ejection fraction were measured by a biplane method of disks in the apical 2- and 4-chamber views (15). The LV sphericity index was calculated as the short-axis diameter in mid-LV region divided by the long-axis diameter at end-systolic phase in the apical 4-chamber view.

**3D TEE. MEASUREMENT OF MITRAL COMPLEX.** 3D TEE was performed using the iE33 with an X7-2t matrix–array transducer (Philips Medical Systems). In the acquisition of 3D echocardiographic data of mitral complex, a 101° × 104° pyramid of gated full-volume mode over 4 beats was used for patients with normal sinus rhythm, and a 3D zoom mode was used for patients with atrial fibrillation. The 3D computer software REAL VIEW (YD Ltd., Nara, Japan) was used to analyze the mitral complex. As previously reported (8,16,17), the 3D data were automatically cropped into 18 radial planes oriented 10° apart (Fig. 1). The mitral annulus in each cropped plane was manually plotted, while the mitral leaflets were traced semiautomatically in each cropped plane. The tips of the PM were captured and marked on cropped planes. The 3D images of the mitral leaflets and annulus were reconstructed from the acquired data, showing the colored con-
figuration of the leaflet curvature and curved annulus, with an alignment of PM tips (Fig. 1). The total leaflet area was assessed at the onset of mitral leaflet closure. The mitral annular area was calculated at midsystole. The tenting volume was calculated as the volume enclosed between the estimated curved annular surface and mitral leaflets at midsystole. To observe the PM displacement, we measured the distance between the tip of the anterior or posterior PM and intervalvular fibrosa (the middle anterior part of the annulus) as the lateral or medial tethering length (TL) in mid systole (Fig. 1). All the measurement values were normalized to body surface area.

MEASUREMENT OF COAPTATION. The 3D data sets were digitally stored and transferred to a workstation with Q-Lab software (Philips Medical Systems) with 3D-Q plug-in for offline analysis. Three simultaneous orthogonal mitral annulus planes and a fourth view showing the orientation of the planes related to volume were presented in multplanar reformatting mode (Fig. 2) (18). Within each of the planar views, the location of intersection with other imaging planes was shown by reference lines, which could be moved to change the orientation and the intersection with other planes. The coaptation length (CL) at the medial, middle, and lateral sites were measured on the optimal long-axis cut plane at midsystole with multiplanar reformating mode (Fig. 3). The middle site was determined as the center of the MV. Then, the medial site was specified as the center of the medial half of the MV. Similarly, the lateral site was specified as the center of the lateral half of the MV. To visualize leaflet coaptation as clearly as possible, the gain was adjusted optimally. Because it was difficult to measure the coaptation length individually due to limited lateral resolution, only the longest coaptation length was measured in this study. Interobserver variabilities of the value of the CL evaluated by means of intraclass correlation coefficients were 0.94 at medial, 0.91 at middle, and 0.96 at lateral lesion. Coaptation area (CA) data were acquired with REAL VIEW (YD Ltd.), and CA evaluated by the following calculation: CA = total leaflet area − closed leaflet area in midsystole (Fig. 4). Total leaflet area was calculated at the onset of mitral leaflet closure in this study. However, it has been demonstrated the mitral leaflet stretches during systole (19,20). Therefore, total systolic leaflet area could be underestimated, leading to the underestimation of CA. Additionally, the coaptation index (CI) was calculated as the ratio
of CA to total leaflet area by the following formula:

$$\text{CI} = \frac{\text{total leaflet area} - \text{closed leaflet area in midsystole}}{\text{total leaflet area}} \times 100$$

(Fig. 4) (8).

**Statistical analysis.** Categorical variables were presented as counts and percentages and compared with the chi-square test. Continuous variables were presented as mean values ± SD. Statistical analysis was performed using the 2-sample unpaired t test for normally distributed data, and the Mann-Whitney U test was used for data that were not normally distributed after testing the normality of the data with the Saphiro-Wilks test. For continuous variables, analysis of variance with post-hoc analysis using the Scheffé test was used to differentiate among 3 regions. The association between the CL and the indexes of LV apparatus was investigated with the linear regression analysis. Correlations between EROA and indexes of coaptation were analyzed by the Spearman rank-order correlation. A p value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS (SPSS, Chicago, Illinois) and Statview (SAS Institute, Cary, North Carolina).

**RESULTS**

Patient characteristics and 2-dimensional echocardiographic parameters are summarized in Table 1. There were no differences in age, sex, and body surface area between those groups. The LV dimen-
sions, LV volumes, and left atrial dimension were significantly larger and LV ejection fractions were lower in the FMR group compared with those in the control group (all p < 0.0001). The elliptical shape of LV becomes more spherical in patients with FMR than in the control subjects (p < 0.0001).

Mitral complex geometry and leaflet coaptation. The mitral complex geometry and leaflet coaptation indexes are summarized in Table 2. The mitral annular area, tenting volume, and TL were significantly larger in patients with FMR than in the control subjects (all p < 0.0001). The leaflet area showed similar increase in patients with FMR (p < 0.0001); however, there were no significant difference in leaflet-to-annular area ratio between the 2 groups (p = 0.09).

In the control group, the CL at the middle site was significantly longer than that at the medial and lateral sites. In contrast, in the FMR group, there were no significant differences among the 3 regions. In patients with LV remodeling, the CL at all 3 sites significantly (all p < 0.0001) and proportionally decreased compared with those in the controls. The CA and CI in patients with FMR were also significantly smaller than those in the control subjects (p = 0.005 and p < 0.0001, respectively).

Because the loss of coaptation was considered as the phenomenon secondary to the PM displacement and annular dilation, we assessed the relationship between CL and TL. The correlations between

| Table 1. Patients’ Clinical and 2-Dimensional Echocardiographic Characteristics |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | FMR Group (n = 44) | Control Group (n = 56) | p Value |
| Men                            | 38 (86)          | 31 (55)          | 0.10 |
| Age, yrs                       | 68 ± 7           | 67 ± 12          | 0.62 |
| Body surface area, m²          | 1.6 ± 0.1        | 1.6 ± 0.2        | 0.94 |
| 2-Dimensional echocardiography |                 |                 |     |
| Left ventricle                 |                 |                 |     |
| Diastolic dimension, mm        | 60 ± 6           | 44 ± 3           | <0.0001 |
| Systolic dimension, mm         | 51 ± 8           | 28 ± 4           | <0.0001 |
| Diastolic volume, ml           | 164 ± 41         | 91 ± 11          | <0.0001 |
| Systolic volume, ml            | 112 ± 39         | 31 ± 10          | <0.0001 |
| Ejection fraction, %           | 33 ± 11          | 66 ± 7           | <0.0001 |
| Sphericity index               | 0.59 ± 0.06      | 0.39 ± 0.05      | <0.0001 |
| Left atrial dimension, mm      | 59 ± 11          | 35 ± 4           | <0.0001 |
| Regurgitant orifice area, cm²  | 0.27 ± 0.19      | —                | —    |

Values are n (%) or mean ± SD.

FMR = functional mitral regurgitation.
Table 2. Geometric Measurements of Mitral Complex and Coaptation

<table>
<thead>
<tr>
<th></th>
<th>FMR Group (n = 44)</th>
<th>Control Group (n = 56)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annular area, cm²/m²</td>
<td>6.0 ± 2.5</td>
<td>4.5 ± 0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Leaflet area, cm²/m²</td>
<td>8.7 ± 1.8</td>
<td>6.7 ± 0.9</td>
<td>&lt;0.0001</td>
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<tr>
<td>Leaflet-to-annular area ratio</td>
<td>1.45 ± 0.16</td>
<td>1.50 ± 0.11</td>
<td>0.09</td>
</tr>
<tr>
<td>Tenting volume, ml/m²</td>
<td>1.3 ± 0.7</td>
<td>0.5 ± 0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tethering length, mm/m²</td>
<td></td>
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<tr>
<td>Medial</td>
<td>23.0 ± 2.2</td>
<td>18.4 ± 2.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lateral</td>
<td>20.5 ± 3.2</td>
<td>17.1 ± 2.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coaptation area, cm²/m²</td>
<td>1.3 ± 0.4</td>
<td>1.6 ± 0.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Coaptation index, %</td>
<td>15.6 ± 3.3</td>
<td>23.6 ± 4.8</td>
<td>&lt;0.0001</td>
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Values are mean ± SD. *p < 0.05 versus medial, †p < 0.05 versus lateral. Abbreviation as in Table 1.

the CL at all 3 sites and the medial TL were negative and significant (Figs. 5A to 5C) (medial $r = 0.55$, $p < 0.0001$; middle $r = 0.57$, $p < 0.0001$; lateral $r = 0.54$, $p < 0.0001$). The correlation between the CL and lateral TL was similarly negative and significant (medial $r = 0.45$, $p < 0.0001$; middle $r = 0.51$, $p < 0.0001$; lateral $r = 0.55$, $p < 0.0001$) (Figs. 5D to 5F). Additionally, the leaflet-to-annular area ratio correlated positively and significantly with regional CLs (medial $r = 0.47$, $p < 0.0001$; middle $r = 0.68$, $p < 0.0001$; lateral $r = 0.51$, $p < 0.0001$).

Significant FMR versus nonsignificant FMR. There were no differences in LV volumes, tethering length, and tenting volume between patients with and without significant FMR in this study population (Table 3). There was also no difference in leaflet area between the 2 groups ($p = 0.64$). Conversely, the annular area was significantly smaller in patients with significant FMR compared with the patients without significant FMR ($p = 0.004$). Therefore, leaflet-to-annular area ratio in patients with significant FMR was smaller than that in patients without significant FMR ($p < 0.0001$), suggesting that annular dilation and insufficient leaflet adaptation to the chronic tethering in patients with global LV remodeling leads to significant FMR. Actually, the coaptation indexes including CL, CA, and CI decreased in patients with FMR (all $p < 0.0001$).

DCM versus ICM. The measurements of 3D mitral complex geometry and leaflet coaptation were analyzed separately for patients with DCM (n = 18) and ICM (n = 26). There was no difference in EROA between the 2 groups (0.28 ± 0.2 cm² vs. 0.26 ± 0.2 cm², $p = 0.66$). Also, no significant differences in the measurements of 3D mitral complex geometry and leaflet coaptation were found between the 2 groups (Table 4).

Figure 5. Correlations Between CL and TL

Negative and significant correlations ($p < 0.0001$) were found between coaptation length (CL) measured on the medial (A), middle (B), and lateral sites (C) and the medial tethering length (TL). The correlations between CL on the medial (D), middle (E), and lateral sites (F) and the lateral TL were similarly negative and significant.
Correlations between leaflet coaptation and MR severity. Spearman rank-order correction analysis showed a significant correlation between EROA and CA (ρ = −0.76, p < 0.0001) or CI (ρ = −0.73, p < 0.0001). The medial CL (ρ = −0.73, p < 0.0001), middle CL (ρ = −0.76, p < 0.0001), and lateral CL (ρ = −0.73, p < 0.0001) were also associated with EROA.

DISCUSSION

Our study shows that: 1) the mitral leaflet coaptation decreased proportionally in patients with FMR related to the bilateral PM displacement, despite increased total leaflet area to compensate for the increased mitral annular area and mitral leaflet tethering; 2) annular area was significantly smaller and leaflet-to-annular area ratio was significantly larger in patients with global LV remodeling who have nonsignificant FMR compared with the patients with significant FMR; and 3) the indexes of coaptation were related to MR severity.

FMR is produced by a complex combination of pathophysiological processes where distorted and spherical LV geometry leads to tethering of the chordae and therefore incomplete leaflet coaptation (8,10,21). In this condition, patients with mitral leaflet tethering have been shown to have larger mitral annular area than the control subjects (10). Similarly, Dal-Bianco et al. (22) demonstrated that mechanical stresses imposed by PM tethering increased mitral MV leaflet area and matrix thickness, with cellular changes suggestive of reactivated embryonic valve development pathways. Therefore, patients with greater valve adaptation to the tethered valve geometry could have more complete leaflet closure and less MR. In our study population, significant MR was observed, despite the enlargement of the leaflet size and the preserved compensated mitral leaflet-to-annular area ratio.

Compared with the patients who had significant FMR, annular area was significantly smaller and leaflet-to-annular area ratio was larger in patients with LV remodeling and global systolic dysfunction who did not have significant FMR. This may be a result of decreased systolic annular contraction and/or inadequate leaflet adaptation to the annular dilation and leaflet tethering caused by the distorted LV geometry, concordant with a previous report (10). Actually, the CLs at all 3 regions decreased significantly in patients with significant FMR than in patients without FMR.

Previous studies using 3D transthoracic echocardiography reported that the degree of mitral valve coaptation in patients with FMR was significantly smaller than that in normal subjects (8,10). Another group demonstrated that the symmetrical papillary muscle displacement led to progressive chordal tethering and decreased coaptation in patients with global LV dysfunction, resulting in predominantly central MR (23,24). In the present study, such decrease in coaptation occurred proportionately and the CL correlated significantly with the displacement of PMs.
In addition, we observed that the CL at medial, middle, and lateral sites, CA, and CI were associated with the MR severity. To further preserve the mitral valvular coaptation, extension of the mitral leaflet for patients with FMR has been successfully performed in the clinical setting (25,26). In cases of progressive ventricular remodeling, however, this reconstructive surgical procedure for the MV has shown limited efficacy. Therefore, surgical procedures targeting the subvalvular apparatus and LV may be required.

**Clinical implications.** A considerable number of patients with ischemic MR could often present with persistent or recurrent MR even after undersized ring annuloplasty (27–30). Such failures of ring annuloplasty emphasize the necessity of procedures targeting the subvalvular apparatus. Recently, Langer et al. (31) reported that the annuloplasty ring plus posterior PM repositioning procedure clinically treated ischemic MR better than an undersized annuloplasty ring alone. However, as suggested in our study and the previous report (17), tethered leaflet in patients with bilateral PM displacement is usually observed not only on the medial side but also on the lateral side, which may necessitate more physiological “chordal relocation” where both papillary heads are repositioning to the annulus (32–34). Therefore, a comprehensive pre-operative assessment including the measurements of the mitral complex and CLs at 3 sites may contribute to the reconstruction of the mitral complex and LV physiologic geometry.

**Study limitations.** Our study has limitations in that it has a lack of patients with regional LV remodeling (e.g., isolated inferior wall-motion abnormality). Therefore, prospective studies are needed to clarify the relationship between the coaptation length and mitral complex apparatus in those patients. Total leaflet area was calculated at the onset of mitral leaflet closure in this study. However, it has been demonstrated that the mitral leaflet stretches during systole (20,21). Therefore, total leaflet area could be underestimated, leading to the underestimation of CA. However, it is not anticipated that will change the relation between measures of coaptation and functional MR outcome.

**CONCLUSIONS**

Despite the increased mitral leaflet size to compensate for the increased mitral leaflet tethering, coaptation decreased significantly in patients with significant FMR. The regional coaptation was related to PM displacement, and the indexes of coaptation were related to MR severity. These results may have implications for surgical strategy for individual patients with FMR.

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