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Title: Advanced echocardiography and clinical surrogates to risk stratify and manage patients with structural heart disease
Issue Date: 2016-04-28
Chapter 4

Leaflet remodeling in functional mitral valve regurgitation: characteristics, determinants and relation to regurgitation severity

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ABSTRACT

Objectives
Recently it has been hypothesized that mitral leaflet remodeling may play a role in the pathophysiology of functional mitral regurgitation (FMR). We investigated the characteristics, determinants and relation of mitral leaflet remodeling to FMR severity.

Methods and Results
3-dimensional transesophageal echocardiographic data of the mitral valve (MV) were studied in 30 patients with FMR ≥grade 3 (≥3), 24 patients with FMR <grade 3 (<3) and 22 controls with normal MV. FMR <3 and ≥3 patients showed leaflet remodeling compared to control subjects with larger overall MV leaflet areas (11.47±3.16 and 9.58±1.99 vs. 7.30±1.57 cm²/m², respectively; all p<0.01). Tenting volume (r²=0.55), LV ejection fraction (r²=0.20), annulus area (r²=0.87) and LV sphericity index (r²=0.25) were correlated with overall MV leaflet area (all p<0.001). Although these correlates were similar between FMR <3 and ≥3 patients (all p>0.05), the overall MV leaflet area was smaller in FMR ≥3 compared to FMR<3 patients (p=0.01), indicating less remodeling despite similar tethering degree. Particularly, coaptation/overall MV leaflet area ratio ≤0.24, reflecting insufficient leaflet remodeling, was associated with FMR ≥3 (area under ROC curve=0.93, sensitivity 90% and specificity 91%). This ratio was independently associated with FMR ≥3 (OR 61.3, 95%CI 9.4-399.9, p<0.001) and showed significant correlation with effective regurgitant orifice area (r²=0.38, p< 0.001).

Conclusion
MV leaflet remodeling in FMR is common and relates to LV function, LV sphericity, MV tenting volume and annulus dilatation. Insufficient leaflet remodeling relative to the mitral annular and LV changes is independently associated with FMR severity.
INTRODUCTION

Functional mitral regurgitation (FMR) affects approximately 30% of patients with ischemic heart disease or dilated cardiomyopathy and yields a dismal prognosis. FMR is a complex problem, comprising dysfunction of a structurally normal mitral valve (MV) secondary to local or global left ventricular (LV) dysfunction with distorted LV geometry. Recent data, however, have challenged the idea of the MV being only an “innocent bystander” in FMR patients. In particular, it was shown that the MV in patients with end-stage heart failure exhibits extracellular matrix changes proportional to annular, atrial and ventricular dimensions and function, including increased fibrosis (collagen), deoxyribonucleic acid (DNA, cellularity) and glycosaminoglycan extent. These alterations coincided with increased leaflet thickness and length, reflecting structural leaflet remodeling. Animal studies have also shown an up-regulation of the extracellular matrix and mitral leaflet adaptation (increased area) as a compensatory response to LV dilatation or loading. More recent studies, using 3-dimensional (3D) echocardiography which is ideally suited for detailed evaluation of MV anatomy and morphology, have shown the presence of MV leaflet remodeling in patients with LV dysfunction and have suggested that inadequate leaflet remodeling may be related to the presence of significant FMR. Data on characteristics, potential determinants and the relationship of MV leaflet remodeling to FMR severity are scarce, however. Therefore, the hypothesis of the present evaluation was to demonstrate whether inadequate leaflet remodeling on 3D echocardiography, expressed as lack of leaflet coaptation relative to annular or LV changes, relates to presence of significant FMR.

METHODS

Patients

Patients with FMR who underwent 3D transesophageal echocardiography were included. FMR was defined as MR due to local or global LV dysfunction and/or remodeling in the absence of macroscopic morphologic abnormalities of the mitral valve. Clinical reasons for transesophageal echocardiography in FMR patients comprised evaluation of severity of valvular dysfunction and specific underlying mechanism (n=35/54), screening for transcatheter mitral valve repair eligibility (n=17/54) or diagnostic work-up before ventricular tachyarrhythmia ablation (n=2/54). A control group included patients with macroscopically normal structural and functional MV who underwent clinically indicated 3D transesophageal echocardiography to exclude cardiac embolism source (n=19/22) or endocarditis (n=3/22). Patients
with aortic valve stenosis, MV stenosis, prior left-sided valve surgery, organic MV disease (prolapse, flail, cleft, rheumatic disease), congenital heart disease, active endocarditis, LV assist device or hypertrophic cardiomyopathy and patients with insufficient image quality were not included.

Clinical characteristics, medication use and heart failure etiology (ischemic versus non-ischemic, including location of prior myocardial infarction) were retrieved from the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands). Patients with FMR were divided into two groups according to the mitral regurgitation grade (FMR<3 versus FMR≥3). MV apparatus geometry and mitral leaflet remodeling were evaluated and compared between groups.

The institutional ethical committee approved this evaluation and waived the need for patient written informed consent for retrospective analysis of clinically collected data.

**2D echocardiography**

All patients underwent 2-dimensional (2D) transthoracic echocardiography in the left lateral decubitus position using commercially available ultrasound machines (Vivid-5, Vivid-7 and E9, GE-Vingmed, Milwaukee, WI) equipped with 3.5 MHz and M5S transducers. 2D-gray-scale and Doppler images were acquired in cine-loop format with ECG-triggering. Off-line analysis of these images was performed on a workstation (EchoPAC 112.0.0, GE Medical Systems, Horten, Norway). LV and left atrial dimensions were assessed as recommended. LV end-diastolic and end-systolic diameters were measured at the parasternal long-axis view. The Simpson’s biplane method was applied to quantify LV volumes and to calculate LV ejection fraction. Left atrial volume was also measured according to the biplane method. All volumes were indexed to body surface area. LV sphericity index was defined as the ratio of end-diastolic mid-ventricular width to length of the LV. Early (E) and late (A) diastolic mitral inflow velocities as well as deceleration time were assessed by pulsed-wave Doppler, placing the sample volume at the tips of the mitral leaflets. Septal mitral annulus velocities (E’) were derived from tissue Doppler recordings and used to calculate the E/E’ ratio. In line with current recommendations, integration of all available qualitative and (semi-)quantitative parameters assessed with 2D echocardiography, including vena contracta width and effective orifice area (EROA) by proximal isovelocity surface area method were evaluated to grade FMR as trivial (1), mild (2), moderate (3) or severe (4). A vena contracta width between 3-4 mm, 5-6 mm and ≥7 mm defined grade 2, 3 and 4 FMR, respectively. In addition, an EROA between 10.0-14.9 mm², 15.0-19.9 mm² and ≥20.0 mm² defined grade 2, 3 and 4 FMR, respectively.
Chapter Four

3D echocardiography

Patients underwent 3D transoesophageal echocardiography using a Philips iE33 ultrasound machine (Philips Medical Systems). 3D datasets of the MV were acquired using full-volume or 3D-zoom mode, comprising a pyramidal volume of approximately 60° by 60°. In order to maximize frame rate, multi-beat (7-14 beats) full-volume acquisitions were performed during breath-hold whenever possible or 1-beat 3D-zoom acquisitions with the sector adjusted to include the MV if the patient could not hold the breath or when presenting with irregular heart rhythm such as atrial fibrillation.

3D mitral valve quantification

3D volumetric datasets of the MV were studied off-line on a workstation (Qlab, Philips Medical Systems, version 9.0) using dedicated commercially available MV Quantification software (MVQ). To maximize spatial and temporal resolution, 3D-full volume acquisitions were preferred over 3D-zoomed acquisitions and mean frame rate was 26 frames/s. Stepwise reconstruction of a 3D-model of the MV was performed by a single experienced operator, blinded to FMR severity (Figure 1A). After selecting the end-systolic frame, multi-plane reformation (MPR) planes were automatically displayed and manually aligned to obtain a bicommisural, outflow tract and short-axis view of the MV. In addition, a 3D volume rendering of the MV is displayed and can be additionally used for identification of anatomic landmarks. The short-axis plane was set at the level of the mitral annulus. The antero-lateral and postero-medial mitral annulus were then indicated on the bicommisural view whereas the anterior and posterior mitral annulus as well as the mitral leaflet coaptation point and the aortic annulus were set at the outflow tract view. An initial 3D-model containing an annular ring and mitral leaflets was then automatically displayed. The mitral annulus on the 3D-model was subsequently refined by indicating additionally 8 pairs of annulus points on sequential MPR rotational cross-sections in the long-axis views and the mitral leaflet commissural points were set on the short-axis MPR image. Subsequently, the mitral leaflets and the coaptation length were manually traced on multiple cross-sections (between 18 to 30) in the outflow tract view, orthogonal to the inter-commissural direction with a minimal distance of 0.17 cm between cross-sections. To correctly identify the coaptation point, the 3D-rendered volume of the MV (surgical en face view) was additionally used. Finally, the 3D model of the MV was displayed and several geometric measurements of the MV were automatically generated (Figure 1B). Lengths, areas and volumes were indexed to body surface area. In particular, the antero-posterior and inter-commissural annular diameter and circumferential annular area were assessed. In addition, the exposed leaflet area of the total MV and
the respective anterior and posterior leaflets, representing the surface exposed to the left atrium, were derived. The overall leaflet area, including the exposed area and coaptation area of each mitral leaflet was also computed. The coaptation area was calculated as the overall leaflet area minus the exposed leaflet area of the total MV. Of note, the anatomic regurgitant orifice area is not excluded from the coaptation area as spatial resolution does not permit its adequate detection. The coaptation length at central level (A2-P2) and the tenting volume comprised between the leaflets and the annular surface area were also measured. Similar to prior reports, the ratio of overall total leaflet/annular area (leaflet/annular area) and coaptation/overall total leaflet area (coaptation/leaflet area) were assessed as measures of leaflet remodeling, relative to the mitral annulus and LV changes.

Statistical analysis
Continuous variables are presented as mean ± SD and compared with the Student T-test or Mann-Whitney U-test, as appropriate. Categorical variables are presented as number and percentages and compared by Pearson chi-square test. Overall comparison among groups was performed by one-way ANOVA with Bonferroni post-hoc testing (for continuous variables with normal distribution), Kruskall-Wallis (for non-normally distributed continuous variables) or Pearson
chi-square (for categorical variables) tests. Correlates of overall total mitral leaflet area were explored with linear regression analysis. In addition binary logistic regression was performed to investigate the univariate associates of significant mitral leaflet remodeling (defined as ≥2 SD of the overall leaflet area of control subjects). A receiver operating characteristic (ROC) curve was subsequently constructed to evaluate the value of the coaptation/leaflet area to predict presence of FMR ≥3. Uni- and multivariate binary logistic regression analyses were in addition performed to identify independent correlates of FMR ≥3, using a backward elimination approach. Odds ratio (OR) and 95% confidence intervals (CI) were obtained. A significance level of p<0.10 qualified for entrance in the multivariate model. Finally the association between coaptation/leaflet area and FMR grade was further explored by linear regression analysis. Intra- and inter observer variability for overall and exposed mitral valve leaflet area was evaluated by intraclass correlation for 15 randomly selected patients (5 control subjects, 5 FMR<3 and 5 FMR≥3 patients). Statistical analyses were performed using the SPSS software version 20.0. (SPSS Inc., Chicago, Illinois). A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Patients
Seventy-six patients were evaluated, including 22 controls (53±15 years old, 64% male), 24 patients with FMR<3 (61±16 years old, 50% male) and 30 patients with FMR≥3 (68±12 years old, 60% male). Characteristics of the control and FMR groups are outlined in Table 1. Control subjects were younger, more likely to be in sinus rhythm, had less diabetes mellitus and were using less cardiovascular medication. Patients with FMR≥3 had lower systolic and diastolic blood pressure and higher prevalence of ischemic heart failure etiology compared to patients with FMR<3. Location of myocardial infarction between patients with ischemic FMR<3 vs. FMR≥3 was however, similar. Cardiovascular medication use was comparable between both groups.

FMR patients had significantly larger LV diameters, LV volumes, LA volume and showed significantly worse LV systolic and diastolic function with higher systolic arterial pulmonary pressures compared to controls.

Mitral leaflet remodeling
Geometric and morphologic characteristics of the mitral annulus and leaflets are listed in Table 2. Patients with FMR had significantly larger annular diameters and
Table 4.1
Baseline patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Controls n=22</th>
<th>FMR&lt;3 n=24</th>
<th>FMR≥3 n=30</th>
<th>p value*</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>14 (64)</td>
<td>12 (50)</td>
<td>18 (60)</td>
<td>0.17</td>
<td>0.46</td>
</tr>
<tr>
<td>Age, years</td>
<td>53 ± 15</td>
<td>61 ± 16</td>
<td>68 ± 12</td>
<td>0.001</td>
<td>0.22</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.95 ± 0.2</td>
<td>1.90 ± 0.2</td>
<td>2.03 ± 0.2</td>
<td>0.08</td>
<td>-</td>
</tr>
<tr>
<td>Sinus rhythm, n (%)</td>
<td>22 (100)</td>
<td>19 (79)</td>
<td>19 (63)</td>
<td>&lt;0.001</td>
<td>0.21</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>130 ± 16</td>
<td>129 ± 26</td>
<td>112 ± 21</td>
<td>0.004</td>
<td>0.015</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>75 ± 10</td>
<td>76 ± 15</td>
<td>65 ± 9</td>
<td>0.002</td>
<td>0.006</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>7 (32)</td>
<td>10 (42)</td>
<td>15 (50)</td>
<td>0.17</td>
<td>0.54</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>1 (5)</td>
<td>4 (17)</td>
<td>11 (37)</td>
<td>&lt;0.001</td>
<td>0.10</td>
</tr>
<tr>
<td>Active/ex-smoker, n (%)</td>
<td>9 (45)</td>
<td>11 (46)</td>
<td>16 (53)</td>
<td>0.82</td>
<td>0.58</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>13 (59)</td>
<td>13 (54)</td>
<td>15 (50)</td>
<td>0.49</td>
<td>0.76</td>
</tr>
<tr>
<td>Ischemic FMR, n (%)</td>
<td>-</td>
<td>12 (50)</td>
<td>25 (83)</td>
<td>-</td>
<td>0.009</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior, septal and/or apical</td>
<td>-</td>
<td>7/12 (58)</td>
<td>15/25 (60)</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Inferior, posterior and/or lateral</td>
<td>-</td>
<td>6/12 (50)</td>
<td>11/25 (44)</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>ß-blocker, n (%)</td>
<td>5 (24)</td>
<td>18 (75)</td>
<td>23 (77)</td>
<td>0.036</td>
<td>0.89</td>
</tr>
<tr>
<td>ACE-inhibitor, n (%)</td>
<td>3 (14)</td>
<td>12 (50)</td>
<td>13 (43)</td>
<td>0.036</td>
<td>0.52</td>
</tr>
<tr>
<td>ARB II, n %</td>
<td>3 (14)</td>
<td>6 (25)</td>
<td>10 (33)</td>
<td>&lt;0.001</td>
<td>0.57</td>
</tr>
<tr>
<td>Diuretic, n (%)</td>
<td>2 (10)</td>
<td>17 (71)</td>
<td>28 (93)</td>
<td>0.014</td>
<td>0.09</td>
</tr>
<tr>
<td>Spironolactone, n (%)</td>
<td>1 (5)</td>
<td>6 (25)</td>
<td>11 (37)</td>
<td>&lt;0.001</td>
<td>0.41</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>15 (75)</td>
<td>13 (54)</td>
<td>22 (73)</td>
<td>0.002</td>
<td>0.20</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>45 ± 6</td>
<td>60 ± 9</td>
<td>65 ± 9</td>
<td>&lt;0.001</td>
<td>0.64</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>26 ± 5</td>
<td>47 ± 9</td>
<td>50 ± 10</td>
<td>&lt;0.001</td>
<td>0.45</td>
</tr>
<tr>
<td>LVEDVI, mL/m²</td>
<td>48 ± 15</td>
<td>99 ± 56</td>
<td>99 ± 41</td>
<td>&lt;0.001</td>
<td>1.00</td>
</tr>
<tr>
<td>LVESVI, mL/m²</td>
<td>17 ± 6</td>
<td>67 ± 47</td>
<td>67 ± 37</td>
<td>&lt;0.001</td>
<td>1.00</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>66 ± 6</td>
<td>36 ± 10</td>
<td>36 ± 14</td>
<td>&lt;0.001</td>
<td>1.00</td>
</tr>
<tr>
<td>LVED sphericity index</td>
<td>0.47 ± 0.1</td>
<td>0.61 ± 0.1</td>
<td>0.62 ± 0.1</td>
<td>&lt;0.001</td>
<td>1.00</td>
</tr>
<tr>
<td>LAVI, mL/m²</td>
<td>25 ± 5</td>
<td>51 ± 18</td>
<td>55 ± 20</td>
<td>&lt;0.001</td>
<td>1.00</td>
</tr>
<tr>
<td>E/A</td>
<td>1.0 ± 0.3</td>
<td>1.7 ± 0.8</td>
<td>2.6 ± 1.0</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>E/E’</td>
<td>11 ± 5</td>
<td>30 ± 12</td>
<td>41 ± 23</td>
<td>&lt;0.001</td>
<td>0.044</td>
</tr>
<tr>
<td>DecT, msec</td>
<td>206 ± 37</td>
<td>167 ± 48</td>
<td>146 ± 48</td>
<td>&lt;0.001</td>
<td>0.29</td>
</tr>
<tr>
<td>MV mean gradient, mmHg</td>
<td>1.2 ± 0.4</td>
<td>1.8 ± 0.9</td>
<td>2.0 ± 1.1</td>
<td>0.008</td>
<td>1.00</td>
</tr>
<tr>
<td>MR grade, n (%)</td>
<td>-</td>
<td>7 (29)</td>
<td>0 (0)</td>
<td>0.003</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 1</td>
<td>-</td>
<td>7 (29)</td>
<td>0 (0)</td>
<td></td>
<td></td>
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<tr>
<td>Grade 2</td>
<td>-</td>
<td>17 (71)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>-</td>
<td>0 (0)</td>
<td>7 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>-</td>
<td>0 (0)</td>
<td>23 (77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR vena contracta, mm</td>
<td>-</td>
<td>3.8 ± 0.7</td>
<td>8.1 ± 1.7</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MR EROA (Pisa), cm²</td>
<td>-</td>
<td>0.12 ± 0.1</td>
<td>0.40 ± 0.1</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAPsyst, mmHg</td>
<td>26 ± 5</td>
<td>37 ± 11</td>
<td>43 ± 14</td>
<td>&lt;0.001</td>
<td>0.14</td>
</tr>
</tbody>
</table>

* for comparison between all patient groups
† for comparison of FMR <3 versus ≥3 patients

area compared with controls. The presence of leaflet remodeling was identified in both FMR groups showing larger overall leaflet area compared to controls. Patients with FMR <3 and ≥3 had a respective relative increase of overall total leaflet area of 57% and 31% compared to controls (both, p<0.001). Significant leaflet remodeling, defined as ≥2 SD overall total leaflet area of control subjects, was respectively observed in 67% (n=16/24) and 37% (n=11/30) of patients with FMR<3 and FMR≥3. The pattern of relative leaflet remodeling was symmetrical for the anterior and posterior mitral leaflets. In patients with FMR<3 the anterior and posterior mitral leaflet areas were increased by 53% and 62% whereas in patients with FMR≥3 these increments were of 31% and 32%, respectively. In addition, symmetrical leaflet remodeling was also noted in patients with infero-posterior myocardial infarction (n=17), showing a 35% and 39% relative increase of the posterior and anterior MV leaflet respectively.

Table 4.2
Mitral valve geometry and leaflet remodeling by 3D echocardiography.

<table>
<thead>
<tr>
<th></th>
<th>Controls n=22</th>
<th>FMR&lt;3 n=24</th>
<th>FMR≥3 n=30</th>
<th>p value*</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANNULUS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP diameter, mm/m²</td>
<td>14.3 ± 1.8</td>
<td>18.0 ± 2.5</td>
<td>16.9 ± 2.3</td>
<td>&lt;0.001</td>
<td>0.18</td>
</tr>
<tr>
<td>IC diameter, mm/m²</td>
<td>18.8 ± 2.8</td>
<td>21.1 ± 3.1</td>
<td>19.6 ± 2.0</td>
<td>&lt;0.001</td>
<td>0.12</td>
</tr>
<tr>
<td>Annulus area, cm²/m²</td>
<td>4.6 ± 1.0</td>
<td>6.7 ± 1.6</td>
<td>6.1 ± 1.2</td>
<td>&lt;0.001</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>LEAFLETS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed leaflet area, cm²/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMVL</td>
<td>3.12 ± 0.65</td>
<td>4.81 ± 1.15</td>
<td>4.37 ± 0.80</td>
<td>&lt;0.001</td>
<td>0.23</td>
</tr>
<tr>
<td>PMVL</td>
<td>2.15 ± 0.52</td>
<td>3.62 ± 1.23</td>
<td>3.16 ± 0.84</td>
<td>&lt;0.001</td>
<td>0.21</td>
</tr>
<tr>
<td>Total (AMVL + PMVL)</td>
<td>5.27 ± 1.12</td>
<td>8.42 ± 2.30</td>
<td>7.53 ± 1.54</td>
<td>&lt;0.001</td>
<td>0.18</td>
</tr>
<tr>
<td>Overall leaflet area, cm²/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMVL</td>
<td>4.13 ± 0.86</td>
<td>6.33 ± 1.59</td>
<td>5.39 ± 1.03</td>
<td>&lt;0.001</td>
<td>0.016</td>
</tr>
<tr>
<td>PMVL</td>
<td>3.17 ± 0.74</td>
<td>5.14 ± 1.62</td>
<td>4.18 ± 1.03</td>
<td>&lt;0.001</td>
<td>0.013</td>
</tr>
<tr>
<td>Total (AMVL + PMVL)</td>
<td>7.30 ± 1.57</td>
<td>11.47 ± 3.16</td>
<td>9.58 ± 1.99</td>
<td>&lt;0.001</td>
<td>0.012</td>
</tr>
<tr>
<td>Coaptation area, cm²/m²</td>
<td>2.03 ± 0.50</td>
<td>3.04 ± 0.97</td>
<td>2.04 ± 0.51</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A2-P2 coaptation L, mm/m²</td>
<td>2.8 ± 0.7</td>
<td>3.2 ± 0.9</td>
<td>2.1 ± 0.40</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leaflet/annular area</td>
<td>1.57 ± 0.09</td>
<td>1.70 ± 0.14</td>
<td>1.59 ± 0.17</td>
<td>0.004</td>
<td>0.013</td>
</tr>
<tr>
<td>Coaptation/ leaflet area</td>
<td>0.28 ± 0.02</td>
<td>0.26 ± 0.03</td>
<td>0.21 ± 0.02</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leaflet/exposed area</td>
<td>1.38 ± 0.05</td>
<td>1.36 ± 0.06</td>
<td>1.27 ± 0.03</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tenting volume, mL/m²</td>
<td>0.74 ± 0.29</td>
<td>2.09 ± 1.13</td>
<td>1.87 ± 1.1</td>
<td>&lt;0.001</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* for comparison among all patient groups
† for comparison of FMR <3 versus ≥3 patients
Correlates of mitral leaflet remodeling

Potential determinants of mitral leaflet remodeling were explored by logistic and linear regression analysis. Larger MV tenting volume (OR 10.04, 95% CI 3.52-28.68, p<0.001), LV sphericity index ≥0.65 (OR 17.00, 95% CI 4.76-60.77, p<0.001) and increased mitral annulus area (OR 1.04, 95% CI 1.02-1.07, p<0.001), all reflecting increased tethering forces, significantly correlated with the presence of significant leaflet remodeling and overall mitral leaflet area (Figure 2). In addition LV ejection fraction was significantly and inversely associated with the presence of significant leaflet remodeling (OR 0.94, 95% CI 0.91-0.97, p<0.001) and overall MV leaflet area (Figure 2).

Leaflet remodeling and mitral regurgitation severity

Significant mitral leaflet remodeling was present in both FMR groups. Importantly, a similar degree of tethering was noted in both groups, shown by comparable MV tenting volumes, annulus dilatation and LV size, shape and function (Table 1 and 2). Less extensive leaflet remodeling, however, was observed in patients with FMR≥3 vs. patients with FMR<3, as reflected by smaller overall total MV leaflet

Figure 4.2
Correlates of total mitral valve leaflet area by linear correlation. LVEF: left ventricular ejection fraction.
area (Table 2; Figure 3). This difference was mainly attributed to smaller coaptation area in patients with FMR≥3 compared with patients with FMR<3, as both groups had comparable exposed leaflet area. The coaptation/leaflet area was preserved (proportional to increased leaflet size) in patients with FMR<3, however, it was significantly decreased in patients with FMR≥3 compared with control patients, reflecting insufficient leaflet remodeling resulting in lack of coaptation reserve to compensate for the requirements of the dysfunctional dilated LV (Figure 4).

The ROC curve analysis showed that coaptation/leaflet area was an accurate predictor of the presence of FMR≥3 with AUC=0.925 (p<0.001) (Figure 5A). In particular a coaptation/leaflet area ≤0.24, indicating a coaptation area ≤24% of the overall total leaflet area, had a sensitivity and specificity of 90% and 91% to predict the presence of FMR≥3, respectively.

As shown in Table 3, the multivariate regression analysis demonstrated that coaptation/leaflet area ≤0.24 is strongly related to the presence of FMR≥3, independently of degree of LV tethering or infarct location in case of ischemic FMR. Coaptation/leaflet area showed a significant inverse correlation with FMR severity (r^2=0.38, p<0.001) (Figure 5B).

Additionally, the leaflet/annular area ratio of patients with FMR≥3 was significantly smaller than patients with FMR<3, suggesting insufficient leaflet remodeling to compensate for the increased annulus size.

**Figure 4.3** Mitral valve remodeling among different groups. Patients with functional mitral regurgitation (FMR) show larger total mitral leaflet area than control subjects (leaflet remodeling). Leaflet area in patients with FMR ≥3 versus <3, however, is smaller, mainly due to smaller coaptation area rather than exposed leaflet area. Insufficient leaflet remodeling resulting in lack of coaptation reserve might prohibit adequate systolic leaflet closure and facilitate occurrence of significant FMR. FMR: functional mitral regurgitation, MV: MV.
Figure 4.4
Examples of mitral valve leaflet remodeling in representative subjects. Panel A: control patient without functional mitral regurgitation (FMR). Patients with mild (Panel B) and severe FMR (Panel C), both secondary to inferior infarction. Note larger mitral valve area (MVA) and coaptation area to MVA ratio in patient with mild versus severe FMR. A: anterior, AL: anterolateral, Ao: aorta, P: posterior, PM: posteromedial.

Figure 4.5
Relation of coaptation to mitral valve leaflet area and severity of functional mitral regurgitation. Panel A: ROC-curve analysis, coaptation/leaflet area ratio ≤0.24 predicts FMR ≥ grade 3 with sensitivity of 90% and specificity of 91%. Panel B: Reduced coaptation/mitral leaflet area ratio correlates linearly to FMR severity. Red dashed line indicates the ROC-curve derived cut-off point of ≤0.24. AUC: area under the curve, EROA: effective regurgitant orifice area, Pisa: proximal isovelocity surface area.
Reproducibility

Intraclass correlation coefficients for overall (total) leaflet area were 0.903 (intra-observer) and 0.947 (inter-observer). For exposed leaflet area measurements, the intraclass correlation coefficients were 0.955 and 0.947 for intra-observer and inter-observer reproducibility, respectively.

DISCUSSION

The present evaluation demonstrated that MV leaflet remodeling is common in FMR, showing a symmetrical involvement of both leaflets, and relates to MV tethering and closing forces. In addition, insufficient MV leaflet remodeling to compensate for annular and LV changes is strongly and independently associated with FMR severity, reflecting a potential therapeutic target for patients with functional MV disease.

Leaflet remodeling evidence

FMR results from an imbalance between valvular closing (LV dysfunction, LV and papillary muscle dyssynchrony and reduced annular contraction) and tethering forces (LV sphericity, papillary muscle displacement, annular dilatation and MV tenting). This imbalance causes relocation of the MV coaptation point more api-
cally and/or posteriorly, thereby restricting the leaflets movement with secondary loss of coaptation and FMR. Therefore FMR is generally regarded as a ventricular problem leading to dysfunction of a structurally normal valve. Differences in FMR severity despite similar tethering degree, however, have been observed. For instance in patients with moderate to severe aortic regurgitation and significant LV remodeling, the prevalence of FMR is surprisingly low. Such observations enforce the idea that the MV itself might develop compensatory adaptations to the chronic stress imposed by the annular and LV changes. Indeed, alterations in biochemical extracellular matrix and increased cellularity in mitral leaflets of humans with LV dysfunction have been reported. This ultra-structural remodeling coincides with increased stiffness and reduced leaflet stretch abilities. In addition, structural mitral leaflet remodeling, including increased mitral leaflet length, area and thickness in response to mitral annular and LV dilatation was observed in animal models of both ischemic and non-ischemic heart failure. Evidence of prospective increase in mitral leaflet size >30% in response to imposed stress and as the result of an active biological process was recently provided by longitudinal animal model studies. The current evaluation also shows that patients with FMR have increased MV area of >30% compared to normal controls, indicating presence of leaflet remodeling. These findings are in line with previous reports on transthoracic or transesophageal 3D echocardiography of the MV, showing relative increases in mitral leaflet area of 23% to 35%. This evidence suggests that in patients with FMR the MV shows structural remodeling and should, therefore, not be regarded as `normal`.

**Characteristics and determinants of leaflet remodeling**

The present evaluation indicates that significant leaflet remodeling (defined as ≥2 SD of the overall leaflet area of control subjects) is prevalent. In addition, a symmetrical pattern of relative enlargement of the posterior compared to the anterior MV leaflet was found, even in patients with ischemic cardiomyopathy with prior infero-posterior myocardial infarction. These findings are in line with a recent finite element analysis in a unique sheep model of the LV and MV after infero-posterior infarction, showing that both anterior and posterior mitral valve leaflets were subjected to similar extent of leaflet stress. As the posterior and anterior MV leaflet have comparable surface areas, one could anticipate that the leaflets show similar extent of enlargement, as shown in current study. Another study using an animal model of non-ischemic cardiomyopathy also reported similar relative increase of the anterior and posterior mitral leaflet area. Other factors than leaflet stress alone, however, might also determine leaflet remodeling. In a recent sheep model with a perforation created in the anterior mitral leaflet, ultra-
structural leaflet remodeling at follow-up was identified, suggesting that isolated MR is able to cause leaflet remodeling of the MV.\textsuperscript{18} However, data on determinants of structural leaflet remodeling in humans are limited. Our findings suggest that both tethering (LV sphericity, annulus size and tenting volume) and closing forces (LV systolic function) are potential determinants of leaflet remodeling. A preserved or higher leaflet/annular ratio in FMR patients compared to controls confirms the idea that leaflet size increases relative to annular dilatation. Other reports have shown similar findings.\textsuperscript{6-8} These results indicate that leaflet remodeling occurs as an adaptive response to annular and LV changes that pose specific requirements to the mitral leaflet size to ensure adequate surface and leaflet coaptation area to prevent from significant FMR.

**Leaflet remodeling and regurgitation severity**

Despite similar tethering and LV remodeling degree, patients with FMR≥3 compared to FMR<3 intriguingly showed less increase in MV area. These results point out that isolated LV remodeling fails to account for the observed FMR variability. The reported variability of FMR prevalence in ischemic patients may suggest that there are other associated pathophysiological factors than regional or global LV remodeling or dysfunction contributing to FMR.\textsuperscript{19, 20} In the present study, although ischemic etiology was significantly more frequent among FMR≥3 patients than in FMR<3 patients, the location of myocardial infarction was not significantly different within the FMR≥3 group. In addition, there was significantly leaflet remodeling difference between groups that was attributed mainly to smaller coaptation area rather than exposed leaflet area. Hence, coaptation/leaflet area (coaptation index) was significantly smaller in FMR≥3 patients versus FMR<3 patients, similar to a prior report on 3D transesophageal echocardiography and comparable to two other studies that mentioned smaller leaflet/exposed (closure) area.\textsuperscript{6-8} These data suggest that leaflet remodeling in FMR≥3 patients is insufficient to compensate for the changes in MV annular and LV dimensions. In particular, the lack of coaptation reserve defined by the ratio coaptation/leaflet area was an independent associate of significant FMR. The presence of limited coaptation reserve <24 % of total MV area was independently related to FMR severity. These findings are in line with the study by Chaput et al. reporting a cut-off value for leaflet/closure area ratio of <1.7 to predict the presence of significant FMR, which reflects <30 % coaptation reserve.\textsuperscript{7} This absolute difference in cut-off value compared to our study might be due to the measurement of mitral valve area at a different time point during the cardiac cycle, to the use of different 3D quantification software and to the use of transthoracic 3D echocardiography characterized by lower spatial resolution, compared to transesophageal 3D echocardiography.\textsuperscript{21}
**Clinical significance**

The current data show, in line with previous reports, that the presence of larger MV leaflets for the same LV tethering degree may protect from FMR.\(^6-8\) These findings might have implications for the treatment of FMR patients, which remains a clinical challenge.\(^2\)

First, elucidating the mechanisms including signaling pathways and triggers that are responsible for leaflet remodeling may help to explain the variability in leaflet remodeling observed in patients despite similar LV dilatation. This knowledge might lead to identification of patients with LV dysfunction that are prone to inadequate MV leaflet remodeling. These patients would represent ideal candidates to undergo biological modification with specific drugs developed to block adverse or stimulate beneficial remodeling of mitral leaflets to prevent from significant FMR.

Second, results of restrictive mitral annuloplasty for FMR overall have been relatively disappointing with high recurrence rates at medium to long-term follow up. In addition, no robust survival benefit has been shown so far for FMR surgery.\(^2\) Current data lend support to the principle of surgical mitral leaflet augmentation plasty, which involves insertion of a pericardial bovine patch into the anterior or posterior MV leaflet in addition to restrictive annuloplasty.\(^22, 23\) MV augmentation plasty increases MV leaflet area, reduces leaflet stress and increases coaptation reserve which might be of paramount importance as the underlying process of adverse LV remodeling potentially continues, imposing specific requirements to the MV area.\(^22, 24\) Given the importance of coaptation reserve that should ideally exceed 24% of the total MV area, as indicated by the current study, this alternative surgical MV repair technique might warrant further study. Small series using posterior (n=44) and anterior (n=25) leaflet augmentation have shown promising results, but long-term results are lacking.\(^22, 25\) The complexity of LV remodeling and FMR, however, probably precludes a single best option to treat FMR that rather requires a tailored approach to the individual patient and MV complex.\(^25\)

**Limitations**

FMR severity assessment is prone to well-known limitations and challenges associated with the functional nature of the valvular regurgitation. Use of a multi-integrative approach, as recommended, partly accounts for these limitations. Mitral leaflet area was assessed at end-systole to ensure evaluation of leaflet coaptation. Therefore a contribution of acute stretch to the measured leaflet area, known to potentially increase leaflet size, can not be excluded.\(^26\) Similar values for leaflet areas compared to our study measured during diastole, however have been reported.\(^6, 7\) In addition, leaflet remodeling in FMR occurs also independently of acute leaflet stretching.\(^5\) Furthermore, LV volumes were derived from 2D echocar-
diographic data. Due to retrospective analysis in a limited number of patients, the present study should be interpreted as hypothesis generating analysis.

CONCLUSION

Mitral leaflet remodeling in patients with FMR is highly prevalent, symmetrical and determined by MV closing and tethering forces. Insufficient leaflet remodeling relative to the annular and LV dilatation causes lack of coaptation reserve and is independently associated with FMR severity. MV leaflets in FMR should not be regarded as `normal` and might represent a biological or interventional therapeutic target.
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