Determinants of the Degree of Functional Mitral Regurgitation in Patients With Systolic Left Ventricular Dysfunction
A Quantitative Clinical Study

Siu F. Yiu, MD; Maurice Enriquez-Sarano, MD; Christophe Tribouilloy, MD; James B. Seward, MD; A. Jamil Tajik, MD

Background—Functional mitral regurgitation (FMR) occurs with a structurally normal valve as a complication of systolic left ventricular dysfunction (LVD). Determinants of degree of FMR are poorly defined; thus, mechanistic therapeutic approaches to FMR are hindered.

Methods and Results—In a prospective study of 21 control subjects and 128 patients with LVD (defined as ejection fraction <50%, mean 31±9%) in sinus rhythm, we quantified simultaneously by echocardiography the effective regurgitant orifice (ERO) of FMR by using 2 methods: mitral deformation (valve and annulus) and left ventricular (LV) global (volumes, stress, function, and sphericity) and local (papillary muscle displacements and regional wall motion index) remodeling. A wide range of ERO (15±6 mm², 0 to 87 mm²) was observed, unrelated to ejection fraction (P=0.32). The major determinant of ERO was mitral deformation, ie, systolic valvular tenting and annular contraction in univariate (r=0.74 and r=20.61, respectively; both P<0.0001) and multivariate (both P<0.0001) analyses, independent of global LV remodeling. Systolic valvular tenting was strongly determined by local LV alterations, particularly apical (r=0.75) and posterior (r=0.70) displacement of papillary muscle, with confirmation in multivariate analysis (both P<0.0001), independent of LV volumes, function, and sphericity.

Conclusions—The presence and degree of FMR complicating LVD are unrelated to the severity of LVD. Local LV remodeling (apical and posterior displacement of papillary muscles) leads to excess valvular tenting independent of global LV remodeling. In turn, excess tenting and loss of systolic annular contraction are associated with larger EROs. These determinants of FMR warrant consideration for specific approaches to the treatment of FMR complicating LVD.

Key Words: echocardiography | heart failure | ventricles | mitral valve | regurgitation

Congestive heart failure is a major cause of cardiac morbidity and mortality1 and is most often due to systolic left ventricular (LV) dysfunction (LVD). Functional mitral regurgitation (FMR) is the regurgitation that occurs despite a structurally normal mitral valve as a consequence of LVD. FMR is poorly characterized because it is often silent,2 but echocardiography has demonstrated its high frequency in LVD.3,4 Severe FMR portends poor hemodynamics5 and poor prognosis,6–9 underscoring the importance of comprehending anatomic determinants of severe FMR.

Although incomplete closure of normal leaflets is the immediate cause of FMR,6,10 the link between LV remodeling and the degree of FMR is not well defined. In experimental in vivo studies, FMR has been attributed to global LV dilatation11 or sphericity.12 More recently, in vitro13 and animal7,8 studies have suggested that complex alterations of spatial relationships between LV and the mitral apparatus may induce severe FMR. In humans, LV sphericalization has been proposed as a potential mechanism of FMR,14,15 but this phenomenon is frequent in LV enlargement with or without regurgitation.16 Similarly, the influence of mitral annulus enlargement on FMR has been disputed.9 These uncertainties are related to the limitations of angiographic17 or color Doppler18 grading of mitral regurgitation (MR) and to the complexity of simultaneous quantification of MR, of mitral deformation, and of global and local LV remodeling. Nevertheless, such an analysis is essential because FMR is a major target of medical19 and surgical treatment.20

Recent advances in noninvasive Doppler echocardiography allow reliable assessment of regurgitant volume11–13 and of the orifice21,22 of MR by combined methods. Quantification of mitral deformation10 and LV remodeling14,15 can be ob-
tained simultaneously. Therefore, we undertook a prospective quantitative study of patients with LVD, with the hypothesis that the effective regurgitant orifice (ERO) of FMR is directly determined by the degree of functional mitral deformation, which in turn is independently associated with local rather than global LV remodeling.

**Methods**

**Eligibility**

Definitions used were as follows: systolic LVD is defined as LV ejection fraction (EF) <50% measured by 2D echocardiography; functional MR, as MR that occurs with a structurally normal valve and that is due to LVD.

Patients were prospectively enrolled. Inclusion criteria were (1) systolic LVD; (2) structurally normal cardiac valves; (3) measurement of aortic, mitral, and LV stroke volumes allowing calculation of MR volume and ERO; (4) anatomic analysis with quantification of LV remodeling and mitral apparatus deformation; and (5) sinus rhythm.

Exclusion criteria were (1) clinical or echocardiographic evidence of other cardiac diseases, such as organic valvular, pericardial, congenital, or infiltrative heart disease; (2) structural mitral lesions, such as valve prolapse or rheumatic disease; (3) more than trace aortic regurgitation; (4) right ventricular alterations resulting in abnormal position or movement of the septum; (5) acute myocardial infarction; (6) suboptimal echocardiographic windows, leading to incomplete quantification of FMR or anatomic assessment; and (7) atrial fibrillation or flutter.

In addition, 21 subjects with normal Doppler echocardiography were included as a control group for quantitative methods of MR and LV remodeling.

**Echocardiographic Measurements**

**Global LV Remodeling**

LV end-diastolic and end-systolic volume indexes (EDVI and ESVI, respectively) and EF were measured by the biapical Simpson disk method. LV length and width were measured, and a dimensionless sphericity index (ratio of length to width) was calculated at end systole and end diastole. End-systolic wall stress was calculated by using blood pressure measurements.

**Quantification of MR**

Two simultaneous methods were used: (1) quantitative Doppler using mitral and aortic stroke volumes and (2) quantitative 2D echocardiography using LV and aortic stroke volumes. These methods were averaged, allowing calculation of regurgitant volume (RVol), regurgitant fraction (RF), and ERO. In 75 patients, the proximal isovelocity surface area method was also used. In patients with no or trivial FMR by color Doppler, RVol and RF were used as calculated, and ERO was assumed as null. Also, jet area and jet/left atrial area ratio were measured.

**Mitral Deformation**

Mitral annular diameter was measured in apical long-axis, 4-chamber, and 2-chamber views at end diastole and end systole, and annular areas and contraction were calculated. Systolic leaflet deformation, defined as valvular tenting area, was measured by the area enclosed between the annular plane and mitral leaflets from the parasternal long-axis view (Figure 1) at early and late systole. The distance between leaflet coaptation and the mitral annulus plane at early and end systole measured displacement of mitral coaptation toward the LV apex.

**Local LV Remodeling**

Asynergy of the LV wall at the papillary muscle attachment was measured as the wall motion score index for the corresponding 8 LV segments. The displacement of papillary muscle was quantified as distances from well-defined anatomic landmarks at early and end systole. From the parasternal short-axis view, the geometric chord defined by the septal insertions and the mid septal perpendicular line were used as references. Lateral and inferior displacements of anterior and posterior papillary muscles were measured as distances from these fixed references. Separation between papillary muscles was directly measured. By use of the long-axis view (Figure 2), apical displacement of the posterior papillary muscle was measured as the distance between the papillary muscle head and the fixed interventricular fibrosa (annular-papillary distance).

**Statistical Analysis**

Data are expressed as mean±SD or percentages. Group comparisons used ANOVA, Student’s t test, or χ² test. For presentation purposes, independent variables were stratified according to ERO level, and their univariate correlations with ERO were summarized. To analyze independent determinants of the degree of FMR, multivariate analysis based on stepwise multiple linear regression (with the ERO and RF as dependent variables and variables measuring mitral deformation as independent variables) was performed. Variables assessing local LV remodeling and then those measuring global LV remodeling were added to the models. A similar multivariate analysis was performed with mitral valvular tenting as a dependent variable and variables measuring local and global LV remodeling as independent variables. The entry criterion in the multivariate analysis was a univariate P<0.10. In 15 patients, a second observer measured the variables of local LV remodeling and mitral deformation to assess interobserver variability. A value of P<0.05 was considered significant.
Global LV remodeling

TABLE 2. Mitral Deformation and Local LV Remodeling in Patients With LVD and Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n=21)</th>
<th>LVD (n=128)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>62±10</td>
<td>65±13</td>
<td>0.20</td>
</tr>
<tr>
<td>Sex, % males</td>
<td>57</td>
<td>65</td>
<td>0.50</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.9±0.3</td>
<td>1.9±0.2</td>
<td>0.52</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>134±19</td>
<td>125±21</td>
<td>0.05</td>
</tr>
<tr>
<td>CI, L - min⁻¹ - m²</td>
<td>2.9±0.4</td>
<td>2.4±0.5</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>Global LV remodeling</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESWS, g/cm²</td>
<td>158±26</td>
<td>271±67</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EDVI, mL/m²</td>
<td>65±10</td>
<td>149±46</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESVI, mL/m²</td>
<td>24±6</td>
<td>106±43</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic L/D</td>
<td>2.5±0.5</td>
<td>1.5±0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic L/D</td>
<td>1.9±0.2</td>
<td>1.4±0.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>EF, %</td>
<td>64±4</td>
<td>31±9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESWS, g/cm²</td>
<td>158±26</td>
<td>271±67</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are mean±SD. BSA indicates body surface area; SBP, systolic blood pressure; CI, cardiac index; L/D, ratio of LV length to width; and ESWS, end-systolic wall stress.

**Results**

**Baseline Characteristics**

The study included 128 patients with LVD in sinus rhythm. LVD was severe but with a wide range (EF 31±9%, range 11% to 49%). FMR also showed a wide range, and 21 patients (16%) had no or trace FMR, whereas in the other 107, the ERO ranged from 3 to 87 mm², RVol ranged from 5 to 121 mL, and RF ranged from 6% to 72%. Respective means in the 128 patients were 15±14 mm², 22±17 mL, and 26±15%. New York Heart Association classes were as follows: I in 22 patients (17%), II in 39 (30%), III in 47 (37%), and IV in 20 (16%). Of 92 patients with coronary angiography, 62 had occlusive disease (>70% stenosis).

Compared with 21 controls, patients with LVD showed no differences in age, sex, or body surface area but significant differences in global and local LV remodeling and mitral deformation (Tables 1 and 2, respectively). The anatomic measurements tended to decrease from early to late systole in patients with LVD (eg, mitral tenting 7.5±1.6 to 6.5±1.4 cm²) and in normal controls (eg, mitral tenting 4.4±0.8 to 3.8±0.6 cm²).

**TABLE 2. Mitral Deformation and Local LV Remodeling in Patients With LVD and Controls**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n=21)</th>
<th>LVD (n=128)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mitral valvular deformation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenting area, cm²</td>
<td>4.4±0.8</td>
<td>7.5±1.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coaptation height, cm</td>
<td>1.6±0.1</td>
<td>2.0±0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic MA area, cm²</td>
<td>6.9±0.8</td>
<td>9.5±1.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic MA area, cm²</td>
<td>4.4±0.7</td>
<td>7.7±1.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MA contact, %</td>
<td>36±6</td>
<td>19±7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Local LV remodeling</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPM posterior D, cm</td>
<td>1.7±0.2</td>
<td>2.4±0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>APM posterior D, cm</td>
<td>2.1±0.2</td>
<td>2.8±0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PPM lateral D, cm</td>
<td>1.5±0.2</td>
<td>2.1±0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>APM lateral D, cm</td>
<td>0.9±0.3</td>
<td>1.4±0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PMs separation, cm</td>
<td>2.5±0.3</td>
<td>3.5±0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PPM-fibrosa D, cm</td>
<td>5.3±0.4</td>
<td>6.6±0.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PMs WMII</td>
<td>1±0</td>
<td>2.2±4.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are mean±SD. MA indicates mitral annulus; PPM, posterior papillary muscle; APM, anterior papillary muscle; D, distance; PMs, papillary muscles; and WMII, wall motion index.
cm² (all P<0.05). However, the magnitude of change was not different between patients and controls (all P>0.10) despite differences in baseline deformation. Because early systolic measurements showed the best correlations with FMR, these values were displayed (Tables 1 and 2).

**Determinants of Degree of FMR**

Patients with LVD were divided into 4 groups according to ERO: no MR (ERO 0, n=21), ERO <10 mm² (n=26), ERO 10 to <20 mm² (n=37), and ERO ≥20 mm² (n=44). These groups also showed significant differences in RVol (3.9±2.7, 11±5, 21±6, and 39±17 mL, respectively; P<0.0001), RF (4.7±3%, 16±6%, 27±7%, and 41±10%; P<0.0001), jet area (0.5±1, 5±3, 7±3, and 13±6 cm²; P<0.0001), and jet/left atrial area ratio (1.9±4%, 13±13%, 26±9%, and 39±11%; P<0.0001).

Comparison between groups (and correlations with ERO) are shown in Table 1 for baseline characteristics and global LV remodeling and in Table 2 for mitral deformation and local LV remodeling. Notably, no significant differences between groups and no significant correlations with ERO were noted for LVEF and wall stress. Higher LV volumes and lower length/diameter ratios were present with higher degrees of FMR, and EDVI displayed the strongest correlation with ERO (r=0.49, P<0.0001; Figure 3), but the other variables showed weaker correlations.

Mitral deformation increased with higher degrees of FMR. The strongest correlation with ERO was observed with the systolic mitral tenting area (r=0.74, P<0.0001; Figure 3). Larger EROs were also associated with larger mitral annular areas and decreased annular contraction (r=-0.61, P<0.0001; Figure 3).

For local LV remodeling, posterior displacements of both papillary muscles were associated with larger EROs (r=0.65 and 0.50, respectively; both P<0.0001), whereas lateral displacements showed weaker associations. Also, apical displacement of papillary muscle, measured as papillary-fibrosa distance, showed significant association with ERO (r=0.55, P<0.0001).

Multivariate analysis of ERO determinants (Table 3) showed the systolic tenting area to be the most powerful predictor (R²=0.53 in all models) in association with annular systolic contraction. Posterior displacement of both papillary muscles also contributed independently to larger EROs. The addition of variables of global LV remodeling did not affect the determinants of ERO. Larger EDVI and lower systolic blood pressure were weakly associated with larger EROs. These results were confirmed by direct comparison of correlations with ERO: those using tenting area and annular contraction were superior to those using EDVI as an independent variable (P=0.0004 and P=0.025, respectively).

Similar independent determinants were noted for RF (Table 3) and the jet/left atrial area ratio, namely, tenting, annular contractility, and posterior displacement of anterior papillary muscle.

Comparing patients with and without coronary disease, similar tenting was observed (7.7±1.7 versus 7.1±1.5 cm², P=0.10), and ANCOVA showed similar regressions between ERO and tenting (P=0.68), ERO and annular contraction (P=0.74), and tenting and apical papillary displacement (P=0.32).

**Determinants of Valvular Tenting**

Systolic valvular tenting is the major determinant of FMR due to LVD. Tenting demonstrated strong correlations with apical papillary muscle displacement (papillary-fibrosa distance, r=0.75, P<0.0001; Figure 4) and with posterior displacement of anterior and posterior papillary muscles (r=0.70 and 0.65, respectively; both P<0.0001; Figure 4). Multivariate analysis showed that tenting was determined by apical and posterior displacement of papillary muscles and by wall motion index of the segments supporting the papillary muscles, independent of global LV remodeling (Table 3). LV volumes, function, or sphericity showed nonsignificant or weak association with tenting (strongest with EDVI, r=0.45; Figure 4) and were not independent determinants of tenting. Direct comparison of correlations with tenting confirmed that...
those obtained with papillary muscle displacements were superior to those obtained with EDVI (both \(P<0.0001\)).

Quality Control
In 42 patients without regurgitation, calculated RVol and RF were extremely low (3.7±2.4 mL and 4.4±2.9%, respectively). Correlations between quantitative Doppler methods and the proximal isovelocity surface area method were excellent for RVol (\(r=0.93, P<0.0001; \text{SEE} 6.5 \text{ mL}\)) and ERO (\(r=0.93, P<0.0001; \text{SEE} 5 \text{ mm}^2\)).

For the 15 patients in whom the mitral and LV remodeling was measured by a second observer, interobserver variability was modest. The correlations between the variables obtained by the 2 observers were as follows: \(r=0.97, P=0.02, \text{and SEE}=0.32 \text{ cm}^2\) for systolic mitral tenting; \(r=0.93, P=0.02, \text{and SEE}=0.42 \text{ cm}\) for papillary-fibrosa distance; and \(r=0.91, P=0.06, \text{and SEE}=0.57 \text{ cm}\) for posterior displacement of papillary muscle.

Discussion
Our prospective series of patients with LVD showed that FMR is frequent but displays a wide range of ERO unrelated to EF. The major determinant of ERO of FMR, to our knowledge reported for the first time in humans, is the systolic mitral valvular tenting and, to a lesser degree, the loss of systolic mitral annular contraction. In turn, mitral systolic tenting is directly determined by apical and posterior papillary muscle displacement. Global LV size, sphericity, stress, and systolic function had no or minimal additional independent association with the degree of FMR and tenting. Local LV remodeling as a determinant of larger tenting and ERO of FMR complicating LVD may be the target of future therapeutic developments.

Importance of FMR
The clinical significance of FMR is frequently underrated because of low murmur intensity and mismatch between severe symptoms and unimpressive RVol and ERO.5,22 Nevertheless, FMR is a major component of LVD, causing pulmonary hypertension and LV volume overload,17,21 which in turn potentiates LV remodeling, a major determinant of the outcome of LVD. Furthermore, FMR is a marker of poor prognosis in LVD that is due to cardiomyopathy17,25 or ischemic disease.20,26

Another hindrance to comprehending the role of FMR in LVD is its sensitivity to loading manipulations.27 Sensitivity to intense treatment19 does not suggest that FMR is insignificant but that FMR is a treatable component of LVD.28 Furthermore, surgical treatment of FMR has been suggested as an important therapeutic option,29 even in cardiomyopathy.30 However, lack of quantitative data on the mechanism of FMR in humans hinders approaches to FMR complicating LVD.

Mechanism of FMR
FMR is not the result of organic mitral lesions but of incomplete closure of normal leaflets.6,10 LV remodeling precedes LVD and FMR,31 but similar LVD may be associated with widely different degrees of FMR. These complex

### TABLE 3. Results of Multivariate Analysis

<table>
<thead>
<tr>
<th></th>
<th>Model Using Variables of Mitral Deformation</th>
<th>Model Adjusted for Local LV Remodeling</th>
<th>Model Adjusted for Global LV Remodeling</th>
</tr>
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<tbody>
<tr>
<td>Determinants of ERO</td>
<td></td>
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<tr>
<td>Tenting area</td>
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<tr>
<td>MA contraction</td>
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<td>Diastolic MA area</td>
<td>0.03</td>
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<tr>
<td>PPM posterior D</td>
<td>...</td>
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<td>0.04</td>
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<tr>
<td>APM posterior D</td>
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<td>0.004</td>
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<tr>
<td>EDVI</td>
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<td>SBP</td>
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<td>(R^2)</td>
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<td>0.0001</td>
<td>0.0001</td>
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<tr>
<td>MA contraction</td>
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<td>0.0001</td>
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<td>(R^2)</td>
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<td>Determinants of mitral tenting area</td>
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<td>PPM-fibrosa D</td>
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<td>0.0001</td>
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<tr>
<td>APM posterior D</td>
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<td>PMs WMI</td>
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<tr>
<td>(R^2)</td>
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<td>0.65</td>
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</table>

Abbreviations as in previous tables.
phenomena require a stepwise analysis, starting with valvular deformations leading to FMR.

Mitral valvular tenting is present in LVD, but tenting degree directly determines ERO of FMR. Tenting is characterized by insufficient systolic leaflet body displacement toward the annulus, with coaptation limited to leaflet tips, resulting in MR. Annular alterations have an adjunct role. Considerable annular dilatation would be required to result in inadequate mitral coaptation, because the ratio of leaflets to the annular surface area is >2. However, insufficient coaptation due to tenting is increased by the loss of systolic annular function, separating the leaflets further. Annular alterations can be palliated by annuloplasty, but mechanisms determining excess tenting warrant consideration to repair FMR.

The degree of LV dysfunction or enlargement is not a primary determinant of regurgitation, and previous studies have attributed FMR to LV sphericalization. However, global sphericalization is common in any LV enlargement and has shown poor correlations with ERO.

Recent pioneering studies performed in vitro or in animal models of LVD have suggested that excessive papillary muscle displacement may generate FMR. This displacement induces valve tethering, which is persistent even in diastole. The present study of humans with a wide range of LVD and FMR shows that apical and posterior displacements of the papillary muscle are the main determinants of tenting and FMR. LV remodeling for any given LV volume may have different local effects and result in different tenting and FMR. For example, in the present series, 2 patients with similar EDVI (202 and 206 mL/m$^2$) and EF (30% and 23%) had very dissimilar apical (7.9 versus 6.4 cm) and posterior (3.5 versus 2.9 cm) displacements of papillary muscle, resulting in widely different tenting areas (8.3 versus 7.7 cm$^2$) and ERO (34 versus 18 mm$^2$). Therefore, local LV remodeling, although related to global LV changes, is the strongest independent determinant of FMR degree and explains its wide range. Lower blood pressure may also contribute to larger ERO through decreased coaptation pressure.

Clinical Implications
That FMR may improve with treatment is well known, but recent data demonstrated that the main mechanism of improvement is a reduction of ERO. The mechanisms of action of medical treatment and the patients benefiting most from treatment have not been defined, underscoring the importance of analyzing FMR and local LV remodeling in future trials.

In the future, surgical correction of apical and posterior displacements of papillary muscles to minimize tenting should probably be combined with annuloplasty and may provide rational approaches to FMR.

Study Limitations
Doppler methods used to quantify FMR may be criticized. In the present study, 2 methods were combined; these methods have been validated and confirmed by our institution. Additionally, the accuracy of stroke volume in patients without regurgitation and excellent correlations with the proximal isovelocity surface area method confirm that the methods used are not a limitation.

For the assessment of LV remodeling, high-resolution imaging allows accurate measurements. For local remodeling, the measures were obtained from appropriately oriented 2D views, with the use of well-defined accepted landmarks and demonstrated high reproducibility.

Conclusions
FMR is a frequent complication of LVD but displays a wide range of degree. Higher ERO of FMR is associated with the loss of annular function and most strongly with excess mitral valvular tenting, which is determined by the degree of local LV remodeling (apical and posterior displacement of papillary muscle), independent of global LV remodeling. These
new quantitative observations should help define new approaches to FMR complicating LVD.

References

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