Mitral Leaflet Adaptation to Ventricular Remodeling
Occurrence and Adequacy in Patients With Functional Mitral Regurgitation

Miguel Chapat, MD; Mark D. Handschumacher, BS; Francois Tournoux, MD; Lanqi Hua, RDCS; J. Luis Guerrero, BS; Gus J. Vlahakes, MD; Robert A. Levine, MD

Background—Functional mitral regurgitation (MR) is caused by systolic traction on the mitral leaflets related to ventricular distortion. Little is known about whether chronic tethering causes the mitral leaflet area to adapt to the geometric needs imposed by tethering, in part because of inability to reconstruct leaflet area in vivo. Our aim was to explore whether adaptive increases in leaflet area occur in patients with functional MR compared with normal subjects and to test the hypothesis that leaflet area influences MR severity.

Methods and Results—A new method for 3-dimensional echocardiographic measurement of mitral leaflet area was developed and validated in vivo against 15 sheep heart valves, later excised. This method was then applied in 80 consecutive patients from 3 groups: patients with normal hearts by echocardiography (n = 20), patients with functional MR caused by isolated inferior wall-motion abnormality or dilated cardiomyopathy (n = 29), and patients with inferior wall-motion abnormality or dilated cardiomyopathy but no MR (n = 31). Leaflet area was increased by 35 ± 20% in patients with LV dysfunction compared with normal subjects. The ratio of leaflet to annular area was 1.95 ± 0.40 and was not different among groups, which indicates a surplus leaflet area that adapts to left-heart changes. In contrast, the ratio of total leaflet area to the area required to close the orifice in midsystole was decreased in patients with functional MR compared with those with normal hearts (1.29 ± 0.15 versus 1.78 ± 0.39, P = 0.001) and compared with patients with inferior wall-motion abnormality or dilated cardiomyopathy but no MR (1.81 ± 0.38, P = 0.001). After adjustment for measures of LV remodeling and tethering, a leaflet-to-closure area ratio <1.7 was associated with significant MR (odds ratio 23.2, 95% confidence interval 2.0 to 49.1, P = 0.02).

Conclusions—Mitral leaflet area increases in response to chronic tethering in patients with inferior wall-motion abnormality and dilated cardiomyopathy, but the development of significant MR is associated with insufficient leaflet area relative to that demanded by tethering geometry. The varying adequacy of leaflet adaptation may explain in part the heterogeneity of this disease among patients. The results suggest the need to understand the mechanisms that underlie leaflet adaptation and whether leaflet area can potentially be modified as part of the therapeutic approach.

(Circulation. 2008;118:845-852.)

Key Words: regurgitation ♦ heart failure ♦ echocardiography ♦ mitral valve ♦ valves

Functional mitral regurgitation (FMR) is a frequent complication of coronary artery disease and dilated cardiomyopathy (DCM) that doubles late mortality.1–4 It is caused by left ventricular (LV) distortion, which leads to displacement of the papillary muscles.5–12 This translates into increased tension on the mitral leaflets during systole, which tethers them below the annulus and impairs coaptation. It is reasonable to expect that mitral leaflet size can play an important role in determining whether mitral regurgitation (MR) actually develops when the leaflets are tethered, but this is as yet unexplored. Little is also known about adaptation of the mitral leaflets to LV remodeling.
FMR is often associated with annular dilatation, which necessarily increases leaflet circumference. Whether this is associated with changes in total leaflet area as an adaptation to chronic tethering that could reduce FMR is not known. In part, this reflects the lack of an imaging technique for measuring mitral leaflet area and its adaptation to changes in the LV.

Our aim was to explore the relationship between leaflet adaptation and the development of MR in the spectrum of patients who present with FMR, which is typically associated with either isolated inferior wall-motion abnormality (IWMA) or DCM. To achieve this goal, we developed a technique for measuring mitral leaflet area in vivo using 3-dimensional (3D) echocardiography. We validated this technique in an animal model and then applied it in patients with FMR to address the hypothesis that leaflet adaptation occurs in patients with chronic tethering but is insufficient to meet the needs for leaflet area imposed by tethering, along with the corollary that leaflet area contributes to the degree of MR.

Methods
Validation Studies
Fifteen healthy Dorsett hybrid sheep were studied by epicardial echocardiography. An apical full-volume data set was acquired over 4 beats with an iE33 3D echocardiography scanner (Philips, Andover, Mass). Animals were euthanized, and the valve was explanted and unfurled on millimetric paper with minimal tension (Figure 1).

Echocardiography
Basic views were obtained with a Philips iE33 scanner and a 5-MHz transducer. Images were analyzed offline with QLab 5.1 (Philips). LV end-diastolic volume, end-systolic volume, and ejection fraction were measured by the biplane Simpson technique. MR was quantified by the width of the proximal jet (vena contracta) in the apical long-axis view.21,22 Tethering distance was assessed in an apical 2-chamber view as the distance between the posterior papillary muscle tip and the contralateral annulus, as described previously.5,23

Leaflet length was measured by 2-dimensional echo from leaflet insertion to tip in the parasternal long-axis view during diastasis before end diastole. Anterior and posterior leaflet thicknesses were measured in the 4-chamber view in the midleaflet at end diastole to minimize the impact of stretch.

Mitral Annulus and Leaflet Surface Area
Images were obtained with an X3 matrix-array transducer (Philips) to acquire 3D volumetric data sets of the mitral valve from 4 heart beats. Leaflet areas were analyzed in midystole and end diastole with custom software running on a personal computer (Omniview, M.D.H.). Total leaflet area can be measured clearly only in diastole, because in systole, the area of each leaflet involved in coaptation cannot be visualized uniformly. Measurement of the diastolic leaflet area also evaluates adaptation when LV pressure and leaflet tension are minimal, without the effects of passive systolic stretch. Therefore, total leaflet area was assessed at full end-diastolic leaflet opening, 1 frame before closure motion.

The valve was traced and photographed, and its area was measured with graphics software (Adobe Photoshop 8.0, Adobe Systems Inc, New York, NY). This study was approved by the local committee on animal care (Institutional Animal Care and Use Committee).

Patient Population
From the out-patient and in-patient lists of the Cardiac Ultrasound Laboratory at our institution, 84 consecutive patients were prospectively recruited after they provided informed consent. Inclusion criteria included a normal heart (n = 24), isolated IWMA (n = 30), and global LV dysfunction (ejection fraction < 35%) with LV dilatation, defined by a subvalvular end-diastolic diameter > 60 mm in the parasternal long-axis view (DCM; n = 30). Patients with mitral prolapse, endocarditis, and aortic valve disease were excluded. Four patients were excluded owing to poor image quality, all in the normal group with nondilated LVs and more limited imaging windows, and the remaining 80 patients constituted the study group (normal, n = 20; IWMA, n = 30; and DCM, n = 30).

To analyze the determinants of FMR, study patients were characterized as having important MR (moderate or greater), defined by a proximal jet width ≥ 4 mm in the apical long-axis view (FMR group, n = 29; 16 with IWMA, 13 with DCM) or no important MR (no MR to mild MR, n = 51; 14 with IWMA, 17 with DCM). Two patients with DCM had atrial fibrillation and were included in the study. The study was approved by the hospital’s institutional review board.

Figure 1. Method of mitral leaflet area measurement (left) showing leaflet reconstruction in a normal beating sheep heart. The area measurement of the explanted valve from the same sheep is shown (right). RV indicates right ventricle; Ao, aorta.

Figure 2. Three-dimensional reconstructions of total mitral leaflet area in diastole (left) and systolic leaflet closure area (right) in a patient with FMR and both systolic and diastolic leaflet tethering.24a Ao indicates aorta; the left atrium is above, LV below, anterior leaflet to the left.
by leaflet tethering.24 The closure area was measured as a continuous
leaflet area in 15 normal sheep. Linear correlation (top) and
Bland-Altman analysis (bottom) are shown.

Figure 3. Validation study of 3D echocardiography vs anatomic
leaflet area in 15 normal sheep. Linear correlation (top) and
Bland-Altman residual analysis (bottom) are shown.

Three-Dimensional Tracing
First, an anatomic reference frame was used to derive a set of views
through the mitral valve rotated around an axis that passed from the
LV apex through the center of the mitral annulus.24 Tracing was
simplified by automatic computation of a set of 9 equiangular image
planes (0° to 180°) that intersected this axis, with the 0° view passing
through the center of the aortic valve (Figure 1). The annular points,
leaflets, and open leaflet tips were traced manually with different
colors for identification on the image planes, which provided 2
leaflet traces per plane for a total of 18 traces. Leaflet tips were
identified as the end of the relatively thick and continuous-appearing
leaflet bodies, assisted by visualization of the valve in cine loop.

An automated computer algorithm connected the individual annu-
lar points to form a closed, 3D annular loop and then computed an
open, tubelike 3D polygonal surface that conformed to the leaflet
traces (Figure 2, left; online-only Data Supplement Appendix). Leaflet area was calculated by summing the elements of this 3D
polygonal surface.

In midsystole, the closed leaflet surface was computed to provide
the closure area as the minimal area of the leaflets necessary to
occlude the orifice on the basis of their 3D shape, which is dictated
by leaflet tethering.24 The closure area was measured as a continuous
surface area separating the left atrial and LV cavities (Figure 2, right;
online-only Data Supplement Appendix); this measurement excludes
the juxtaposed leaflet surface portions that meet in systole but do not
separate the 2 cavities. The regurgitant orifice itself is not visualized
directly and therefore is not excluded from this area; the closure area is
thus the area necessary for the leaflets to completely close the orifice
between the 2 cavities. The normal surplus of leaflet area translates into
a total leaflet area-to-closure area ratio well above 1.25 Finally, mitral
annular area was calculated as the projection of the annular trace onto its
average or least-squares plane.24

To test whether leaflet area increased relative to changes in the left
side of the heart, we calculated the ratio of leaflet to annular area,
both in diastole. To assess the adequacy of leaflet compensation, we
calculated the ratio of total leaflet area to leaflet closure area.

Statistical Analysis
Measurements of leaflet size (area, length, and thickness) were made
by an observer who was blind to the patient’s group (presence or
absence of FMR not seen on 3D leaflet acquisitions). Valve area and
lengths were consistently measured by 1 physician with advanced
echocardiographic training, and variability was compared with
another comparably trained physician; both were experienced with
3D echocardiographic navigation and with the software. Leaflet
thickness was consistently measured by 1 cardiac sonographer with
10 years experience.26

Validation of the leaflet area measurement was performed by
linear regression between anatomic ex vivo measurements and
echocardiographic measurements; agreement was assessed by Bland-
Altman analysis and paired t test. Intraobserver and interobserver
(2 independent readers) variability was also assessed by Bland-
Altman analysis. In addition, interobserver variability was measured by
κ-coefficient between the 2 readers. For continuous variables,
patient groups were compared with 1-way ANOVA and, for pairwise
comparisons, Student-Newman-Keuls tests. A linear regression
model to explain variations in MR by proximal jet width was built
with LV end-systolic volume, LV ejection fraction, annular area,
leaflet area–to–annular area ratio, tethering distance, and patient age.
Those variables were chosen from the univariate analysis for the
prediction of MR proximal jet width. Finally, a logistic regression
model was built to predict the development of important (moderate
or more) MR (proximal jet width ≥4 mm) based on dichotomized
variables: LV dilatation (end-systolic volume >80 mL), LV dys-
function (ejection fraction <35%), annular dilatation (projected
annulus at end systole >9.0 cm²), tethering distance >3.8 cm, and
low leaflet-to–closure area ratio (<1.7). These thresholds were
chosen from observation of the frequency of important MR along the

Table 1. Patient Demographic Characteristics and
Basic Echocardiography

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>FMR (n=29)</th>
<th>No MR (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=20)</td>
<td>(IWMA n=16, DCM n=13)</td>
<td>(IWMA n=14, DCM n=17)</td>
</tr>
<tr>
<td>Age, y†</td>
<td>53±18</td>
<td>60±17</td>
<td>55±15</td>
</tr>
<tr>
<td>Female gender, n (%)‡</td>
<td>8 (40)</td>
<td>9 (31)</td>
<td>11 (35)</td>
</tr>
<tr>
<td>BSA, m†</td>
<td>1.81±0.20</td>
<td>1.89±0.1</td>
<td>1.90±0.15</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>68±9</td>
<td>75±12*</td>
<td>78±13*</td>
</tr>
<tr>
<td>SBP, mm Hgt†</td>
<td>120±14</td>
<td>117±19</td>
<td>123±23</td>
</tr>
<tr>
<td>DBP, mm Hgt‡</td>
<td>66±12</td>
<td>65±11</td>
<td>68±11</td>
</tr>
<tr>
<td>EF, %</td>
<td>60±7</td>
<td>33±9*</td>
<td>38±9‡</td>
</tr>
<tr>
<td>EDV, mL</td>
<td>82±30</td>
<td>155±28*</td>
<td>125±30‡</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>34±17</td>
<td>109±32*</td>
<td>80±28‡</td>
</tr>
<tr>
<td>PJW, cm</td>
<td>0.05±0.08</td>
<td>0.55±0.12‡</td>
<td>0.15±0.10§</td>
</tr>
<tr>
<td>Tethering distance, cm</td>
<td>3.45±0.43</td>
<td>4.20±0.45*</td>
<td>4.00±0.45‡</td>
</tr>
<tr>
<td>Diastolic annular area, cm²</td>
<td>7.5±0.8</td>
<td>10.4±1.3*</td>
<td>9.9±2.0*‡</td>
</tr>
</tbody>
</table>

BSA indicates body surface area; HR, heart rate; SBP, systolic blood
pressure; DBP, diastolic blood pressure; EDV, end-diastolic volume; ESV,
end-systolic volume; and PJW, proximal jet width.

Values are expressed as mean ±SD.
*P<0.05 vs normal group.
†No statistically significant difference among groups (P=NS).
‡No statistically significant difference between patients with and without MR
(P=NS).
§P<0.05 for MR vs no MR.
distribution of the predicting variables, with identification of natural cutoffs, and because of their association with FMR on the basis of widely accepted criteria and a literature search (tethering distance). Analyse was performed with SAS 9.1 (SAS Institute, Cary, NC). Values are reported as mean ± SD.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Validation Studies

Correlation between anatomic measurements and echocardiography-derived leaflet area is shown in Figure 3 ($R^2=0.86$, $P<0.0001$, $\text{SEE}=1.24$). Differences from anatomic data were not significantly different from 0 (mean residual $0.51\pm1.15$, $P=0.71$). The average residual was $-0.13\pm0.51$ ($P=0.85$ versus 0) for intraobserver variability and $0.24\pm1.10$ ($P=0.79$ versus 0) for interobserver variability. The $\kappa$-value was 0.78, which suggests high interrater correlation.

Patient Population

Patient characteristics are shown in Table 1. No significant age difference was found among groups. Ejection fraction was significantly lower and LV volumes and annular area were higher in all disease groups compared with the group with normal hearts. Annular area increased by $29\pm5\%$ ($P=0.003$) in patients with important MR and by $21\pm6\%$ ($P=0.01$) in patients without MR compared with the normal group.

Leaflet Area and LV Remodeling

Total leaflet area increased by $32.5\pm19.2\%$ ($P<0.0001$) in patients with important (moderate or more) MR (pooled IWMA and DCM) versus normal hearts and by $37.5\pm21.0\%$ ($P<0.0001$) in patients with LV abnormalities but without significant MR (no MR to mild MR, $P=0.9$ versus MR; Figure 4). Leaflet area likewise increased when normalized to body surface area in patients with left-heart disease compared with normal hearts (normal $8.3\pm1.6\,\text{cm}^2/\text{m}^2$, FMR $10.5\pm2.2\,\text{cm}^2/\text{m}^2$, $P=0.001$; LV abnormalities but no important FMR $9.8\pm1.9\,\text{cm}^2/\text{m}^2$, $P=0.03$ versus normal).

In patients with DCM, patients without MR had larger leaflet areas than those having MR (DCM but no MR $22.2\pm2.0\,\text{cm}^2$, DCM plus MR $20.2\pm2.3\,\text{cm}^2$, $P=0.03$); no significant differences in LV ejection fraction or volumes were found between DCM patients with and those without MR. Leaflet thickness was increased from normal in all disease groups except for patients with IWMA but no MR (Table 2). In patients with IWMA, although leaflet area was not significantly different in patients with and without MR (Table 2), those with MR had a lower ejection fraction ($35\pm7\%$ versus $42\pm7\%$, $P=0.05$), higher end-systolic volume ($95\pm23$ versus $77\pm20\,\text{mL}$, $P=0.05$), and larger annular area ($P<0.05$), which indicated greater LV remodeling. In contrast to leaflet area, anterior and posterior leaflet 2-dimensional lengths were not significantly different in patients with and without MR (Table 2), those with MR had a lower ejection fraction ($35\pm7\%$ versus $42\pm7\%$, $P=0.05$), higher end-systolic volume ($95\pm23$ versus $77\pm20\,\text{mL}$, $P=0.05$), and larger annular area ($P<0.05$), which indicated greater LV remodeling. In contrast to leaflet area, anterior and posterior leaflet 2-dimensional lengths were not significantly different in patients with and without MR (Table 2), those with MR had a lower ejection fraction ($35\pm7\%$ versus $42\pm7\%$, $P=0.05$), higher end-systolic volume ($95\pm23$ versus $77\pm20\,\text{mL}$, $P=0.05$), and larger annular area ($P<0.05$), which indicated greater LV remodeling. In contrast to leaflet area, anterior and posterior leaflet 2-dimensional lengths were not significantly different in patients with and without MR (Table 2), those with MR had a lower ejection fraction ($35\pm7\%$ versus $42\pm7\%$, $P=0.05$), higher end-systolic volume ($95\pm23$ versus $77\pm20\,\text{mL}$, $P=0.05$), and larger annular area ($P<0.05$), which indicated greater LV remodeling. In contrast to leaflet area, anterior and posterior leaflet 2-dimensional lengths were not significantly different in patients with and without MR (Table 2), those with MR had a lower ejection fraction ($35\pm7\%$ versus $42\pm7\%$, $P=0.05$), higher end-systolic volume ($95\pm23$ versus $77\pm20\,\text{mL}$, $P=0.05$), and larger annular area ($P<0.05$), which indicated greater LV remodeling. In contrast to leaflet area, anterior and posterior leaflet 2-dimensional lengths were not significantly different in patients with and without MR (Table 2), those with MR had a lower ejection fraction ($35\pm7\%$ versus $42\pm7\%$, $P=0.05$), higher end-systolic volume ($95\pm23$ versus $77\pm20\,\text{mL}$, $P=0.05$), and larger annular area ($P<0.05$), which indicated greater LV remodeling. In contrast to leaflet area, anterior and posterior leaflet 2-dimensional lengths were not significantly different in patients with and without MR (Table 2), those with MR had a lower ejection fraction ($35\pm7\%$ versus $42\pm7\%$, $P=0.05$), higher end-systolic volume ($95\pm23$ versus $77\pm20\,\text{mL}$, $P=0.05$), and larger annular area ($P<0.05$), which indicated greater LV remodeling. In contrast to leaflet area, anterior and posterior leaflet 2-dimensional lengths were not significantly different in patients with and without MR (Table 2), those with MR had a lower ejection fraction ($35\pm7\%$ versus $42\pm7\%$, $P=0.05$), higher end-systolic volume ($95\pm23$ versus $77\pm20\,\text{mL}$, $P=0.05$), and larger annular area ($P<0.05$), which indicated greater LV remodeling.

As shown in Figure 5, the leaflet-to–annular area ratio was similar in all groups, including normal patients, maintaining a relatively constant ratio of 1.95±0.24. This suggests that

Table 2. Mitral Valve Dimensions in Patients With Normal Hearts, IWMA, and DCM, With and Without MR

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=20)</th>
<th>IWMA–MR (n=16)</th>
<th>IWMA–No MR (n=14)</th>
<th>DCM–MR (n=13)</th>
<th>DCM–No MR (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL length, mm†</td>
<td>2.43±0.34</td>
<td>2.65±0.29</td>
<td>2.53±0.40</td>
<td>2.75±0.40</td>
<td>2.41±0.19</td>
</tr>
<tr>
<td>PL length, mm†</td>
<td>1.14±0.15</td>
<td>1.36±0.20</td>
<td>1.38±0.18</td>
<td>1.23±0.21</td>
<td>1.27±0.09</td>
</tr>
<tr>
<td>AL thickness, mm</td>
<td>1.59±0.21</td>
<td>2.05±0.20*</td>
<td>1.71±0.21$\text{§}$</td>
<td>2.22±0.30*</td>
<td>1.95±0.31*</td>
</tr>
<tr>
<td>PL thickness, mm</td>
<td>1.66±0.21</td>
<td>2.14±0.22*</td>
<td>1.72±0.22$\text{§}$</td>
<td>2.21±0.25*</td>
<td>2.04±0.30*</td>
</tr>
<tr>
<td>Total valvular area, cm²</td>
<td>15.0±2.3</td>
<td>19.6±2.5*</td>
<td>18.6±2.5$\text{‡}$</td>
<td>20.2±2.3*</td>
<td>22.2±2.0$\text{§}$</td>
</tr>
<tr>
<td>Diastolic annular area, cm²</td>
<td>7.5±0.8</td>
<td>10.4±0.8*</td>
<td>8.4±0.9$\text{§}$</td>
<td>10.5±0.9*</td>
<td>11.0±1.2$\text{‡}$</td>
</tr>
</tbody>
</table>

AL indicates anterior leaflet, PL, posterior leaflet.
†$P<0.05$ vs normal.
*No statistically significant difference among groups ($P=\text{NS}$).
§$P<0.05$ for MR vs no MR within the IWMA or DCM patient groups.
$\text{‡}$ $P<0.05$ for MR vs no MR within the IWMA or DCM groups.
leaflet adaptation correlates with annular dilatation. In contrast, the leaflet-to–closure area ratio was strongly decreased in patients with MR (1.29±0.15 versus 1.78±0.39, \(P=0.0001\)) but not in patients with LV disease but no MR (1.81±0.38), which suggests sufficient adaptation to chronic tethering in patients without MR but incomplete adaptation in patients who develop MR.

**Linear and Logistic Regression Models**

When adjusted for LV size, LV function, annular area, tethering distance, and patient age, the ratio of leaflet to closure area was a significant predictor of MR severity by proximal jet width (linear regression \(r^2=0.93, b=0.19, P=0.04\)). As shown in Table 3, all dichotomized variables included in the multiple variable logistic regression model were significantly associated with the development of important MR by univariate analysis. A leaflet-to–closure area ratio less than 1.7 independently predicted the presence of moderate to severe MR (odds ratio 23.2, 95% confidence interval 2.0 to 49.1, \(P=0.02\)) after adjustment for dilated LV, poor LV function, dilated annulus in midsystole, tethering length, and type of disease (DCM versus IWMA).

**Discussion**

Given that FMR is caused by leaflet tethering to displaced papillary muscle and annular attachments, variation in leaflet size may be an important determinant of whether the valve is actually insufficient. Anatomists have long taught that the mitral valve has a substantial surplus in area relative to the annular orifice, which allows the heart to adapt to volume overload without developing MR.\(^{25,27,28}\) In LV dysfunction, however, the leaflet surface is displaced below the annulus, which increases the closure area necessary to prevent regurgitation. It has been suggested that in this condition, the leaflets may elongate in response to the stresses imposed by increased tethering.\(^{19,20}\) Surprisingly, however, little is known about such proposed elongation.

Until now, noninvasive methods have not been available to address this question of leaflet adaptation in vivo. This would be required not only to measure total leaflet area in situ without extraneous stretch but especially to relate total area to the closed systolic surface area of the tethered leaflets and to the degree of MR, which can only be measured in vivo. Therefore, we developed an algorithm for reconstructing leaflet area by real-time 3D echocardiography and validated it against excised specimens. This method for the first time allowed measurement of leaflet area in the beating heart under physiological loads.

This algorithm was then applied in patients with the classic scenarios in which FMR develops, segmental inferior-wall and global LV dysfunction. The results showed that mitral

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Logistic Regression</th>
<th>Multiple Variable Logistic Regression*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient group DCM vs IWMA</td>
<td>3.95 (1.8–9.7) P=0.003</td>
<td>1.7 (0.5–6.5) P=0.4108</td>
</tr>
<tr>
<td>EF &lt;35%</td>
<td>10.8 (2.58–43.5) P=0.0011</td>
<td>4.9 (0.3–18.0) P=0.7303</td>
</tr>
<tr>
<td>Annular dilation (&gt;9 cm(^2))</td>
<td>12.2 (2.86–52.0) P=0.0007</td>
<td>2.0 (0.2–18.1) P=0.1</td>
</tr>
<tr>
<td>ESV &gt;80 mL</td>
<td>18.5 (4.3–83.3) P=0.0001</td>
<td>3.7 (0.3–47.0) P=0.3098</td>
</tr>
<tr>
<td>Leaflet area-to–closure area ratio &lt;1.7</td>
<td>35.7 (4.27–333.3) P=0.001</td>
<td>23.2 (2.0–49.1) P=0.02</td>
</tr>
<tr>
<td>Tethering length &gt;3.9 cm</td>
<td>6.5 (1.72–25.0) P=0.006</td>
<td>2.2 (0.2–23.0) P=0.5225</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval; EF, ejection fraction; and ESV, end-systolic volume.

*Wald \(P=0.03\).
leaflet area does increase by up to 35% on average in patients with IWMA and DCM compared with normal subjects. This degree of leaflet area augmentation exceeds that which can be explained by passive stretching of the valve, and moreover, it is measured in the unstretched leaflets during diastole. Interestingly, the ratio of leaflet to annular cross-sectional area was relatively constant among patients and normal subjects; this suggests that the valve enlarges predominantly through expansion of its annular circumference rather than by elongation from insertion to tip. These lengths, measured through the center of the valve in a long-axis view, were not different among patient groups and normal subjects for either leaflet (Table 2), which contributes to the visual impression of lack of adaptation based on 2-dimensional images in clinical experience.

On the other hand, this leaflet area adaptation is often insufficient to meet the need for an expanded leaflet closure surface demanded by the tethered leaflet geometry. The normal surplus of leaflet relative to the closure area is substantially smaller in patients with FMR, which allows greater opportunities for insufficiency (Figure 5). The regression analysis further shows that variation in leaflet area relative to closure area independently contributes to variation in the degree of MR, so that patients with relatively larger leaflets have less MR.

The nearly 2-fold leaflet surplus relative to annular area in the present study is comparable to that described anatomically by Chiechi et al. Although Hueb et al also described increased leaflet area in autopsy specimens of patients with FMR, their values were roughly 50% of those described in vivo, which was possibly related to valve fixation, but their values were also roughly equivalent to the annular area, as opposed to the normal nearly 2-fold surplus, because they photographically measured the projected leaflet area viewed through the annulus as opposed to planimetrizing the excised leaflet area. Measurement of excised areas cannot relate to the degree of MR, which allows greater opportunities for insufficiency (Figure 5). The regression analysis further shows that variation in leaflet area relative to closure area independently contributes to variation in the degree of MR, so that patients with relatively larger leaflets have less MR.

In summary, therefore, mitral leaflet area undergoes long-term adaptation in states of LV dysfunction in parallel with annular area, but in patients with FMR, such adaptation is insufficient to meet the needs for increased leaflet area imposed by the tethered leaflet configuration. Furthermore, variation in leaflet area in relation to the required closure area is an important determinant of the degree of MR. Finally, the results suggest the need to understand the mechanisms that underlie leaflet adaptation and whether leaflet area can potentially be modified as part of the therapeutic approach to FMR.

Limitations and Future Directions
In the present study, we measured total leaflet area in diastole. Although total systolic leaflet area would also have been of interest, the inability to measure the coapted leaflet portions unambiguously where the leaflets are juxtaposed limits this measurement.

The diastolic, open leaflet area, however, has the advantage of providing a measure of long-term leaflet adaptation without the superimposed effects of systolic stretch. The observation of fairly constant diastolic leaflet length also indicates that we are measuring long-term adaptation of leaflet size as opposed to a short-term stretch, which predominantly increases leaflet length. Three-dimensional echocardiography has recognized limitations of spatial and temporal resolution. Careful review of cine loops in multiple imaging planes perpendicular to the annulus helped define the annular hinge points. The accuracy of any surfacing algorithm is subject to the size of the mesh elements and the degree of smoothing. Trace irregularity can increase calculated area relative to actual area. To minimize this effect after the initial tracing, the 3D reconstruction of the valve was reviewed carefully for consistency; also, the algorithm for modeling the wire mesh surface used a distance-weighted averaging of neighboring points to avoid sharp angular changes of adjacent tiles that would overestimate the surface area.

Of note is that the increase in leaflet area compared with normal hearts was comparable in patients with localized versus global LV dysfunction, despite typical differences in LV size in those 2 groups. Thus, leaflet area increase cannot simply be ascribed to global LV dilatation but relates more closely to localized tethering and annular changes.

In summary, therefore, mitral leaflet area undergoes long-term adaptation in states of LV dysfunction in parallel with annular area, but in patients with FMR, such adaptation is insufficient to meet the needs for increased leaflet area imposed by the tethered leaflet configuration. Furthermore, variation in leaflet area in relation to the required closure area is an important determinant of the degree of MR. Finally, the results suggest the need to understand the mechanisms that underlie leaflet adaptation and whether leaflet area can potentially be modified as part of the therapeutic approach to FMR.

Acknowledgment
We thank Shirley Sims for her expert editorial assistance.

Sources of Funding
This study was supported by grant 07CVD04 from the Fondation Leducq, Paris, France, for the Transatlantic MITRAL Network of Excellence, and by grants R01 HL38176 and K24 HL67434 of the National Institutes of Health, Bethesda, Md.

Disclosures
None.
References


---

**CLINICAL PERSPECTIVE**

Left ventricular remodeling after myocardial infarction or in dilated cardiomyopathy creates mismatch between mitral leaflet and ventricular size, which leads to ischemic mitral regurgitation, a source of increased heart failure and mortality. We explored whether the valve itself adapts to the stresses imposed by the dilating ventricle. Three-dimensional echocardiography, validated against excised valves, measured diastolic leaflet area in 80 patients and control subjects. Leaflet area was an average of 35% greater in patients with left ventricular dysfunction than in control subjects. Leaflet area showed comparable adaptation to annular area in all groups (nearly 2-fold ratio). However, leaflet area was a strong independent predictor of mitral regurgitation, and patients with mitral regurgitation had reduced ratios of total leaflet area to the tented leaflet area required to close the annular orifice in systole. The valve therefore adapts to the increased size of remodeled ventricles, but the degree of adaptation may be insufficient to prevent mitral regurgitation by meeting the geometric demands imposed on the stretched leaflets. Understanding the mechanisms of mitral valve adaptation can potentially provide new therapeutic targets.
Mitral Leaflet Adaptation to Ventricular Remodeling: Occurrence and Adequacy in Patients With Functional Mitral Regurgitation
Miguel Chaput, Mark D. Handschumacher, Francois Tournoux, Lanqi Hua, J. Luis Guerrero, Gus J. Vlahakes and Robert A. Levine

Circulation. 2008;118:845-852; originally published online August 4, 2008; doi: 10.1161/CIRCULATIONAHA.107.749440

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/118/8/845

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2008/08/18/CIRCULATIONAHA.107.749440.DC2
http://circ.ahajournals.org/content/suppl/2008/08/08/CIRCULATIONAHA.107.749440.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/
1) Form annular loop, leaflet tip loop, calculate the loop centroids and orient traces so centroids align with the Z-axis

2) Setup equiangular array of planes passing through z-axis and compute intersections with annular and leaflet tip loops.

3) Construct evenly spaced rays perpendicular to Z-axis between local annulus and leaflet tip for each angle and adjust ray length to fit traces.

4) Connect adjacent grid points 3D polygonal mesh from grid values and sum triangular facet areas.
1. Form annular loop and fit to LSQ Plane
2. Define grid of (64) equiangular rays from centroid in XY-plane
3. Adjust ray length to fit annular boundary
4. Partition rays into (32) equidistant segments to define 2D grid in XY-plane
5. Assign regional leaflet height (Z) to grid points
6. Interpolate unassigned grid values
7. Create Polygonal mesh surface and compute area
1) Form annular loop, leaflet tip loop, calculate the loop centroids and orient traces so centroids align with the Z-axis.

2) Setup equiangular array of planes passing through z-axis and compute intersections with annular and leaflet tip loops.

3) Construct evenly spaced rays perpendicular to Z-axis between local annulus and leaflet tip for each angle and adjust ray length to fit traces.

4) Connect adjacent grid points 3D polygonal mesh from grid values and sum triangular facet areas.

Open leaflets
1. Form annular loop and fit to LSQ Plane
2. Define grid of (64) equiangular rays from centroid in XY-plane
3. Adjust ray length to fit annular boundary
4. Partition rays into (32) equidistant segments to define 2D grid in XY-plane
5. Assign regional leaflet height (Z) to grid points
6. Interpolate unassigned grid values
7. Create Polygonal mesh surface and compute area

Atrium

Ventricle