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Mitral Valve Enlargement in Chronic Aortic Regurgitation as a Compensatory Mechanism to Prevent Functional Mitral Regurgitation in the Dilated Left Ventricle

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Abstract:

Objectives: To test the hypothesis that mitral valve (MV) enlargement occurring in chronic aortic regurgitation (AR) prevents functional mitral regurgitation (FMR).

Background: Chronic AR causes left ventricular (LV) dilatation, creating the potential for FMR. However, FMR is typically absent during compensated AR despite substantial LV enlargement. Increased mitral leaflet area has been identified in AR, but it is unknown whether increased MV size can represent a compensatory mechanism capable of preventing FMR.

Methods: Database review of 816 patients with at least moderate AR evaluated the prevalence of FMR. A total of 90 patients were enrolled prospectively for 3D echocardiography (30 AR, 30 FMR and 30 controls) to assess MV geometry including total leaflet area.

Results: FMR was present in 5.6% of AR patients by database review. Prospectively, only one AR patient had >mild FMR despite increased LV end-diastolic volume (82±22, 86±23 and 51±12 cm³/m² for AR, FMR versus controls, p<0.01), and similar sphericity index, annular area and tethering distances compared to FMR. Total MV area was largest in AR (31.3% greater than normal), increasing significantly more than in FMR. The ratio of valve size to closure area was maintained in AR while decreases in this ratio and LVEF independently predicted FMR.

Conclusion: FMR prevalence is low in chronic AR. MV leaflet area is significantly increased compared to controls and FMR patients, preserving a normal relation to the area needed for closure in the dilated LV. Understanding the mechanisms underlying this adaptation could lead to new therapeutic interventions to prevent FMR.

Keywords: Aortic regurgitation, functional mitral regurgitation, valvular disease.

Abbreviations list:

MR: Mitral regurgitation
LV: Left ventricle
AR: Aortic regurgitation
3D: Three-dimensional
MV: Mitral valve
Functional mitral regurgitation (MR) is a common complication of cardiomyopathies associated with higher mortality(1-4). Its mechanisms have been related to left ventricular (LV) enlargement and distorted shape, restricting mitral valve (MV) closure(5-8). However, LV remodeling alone fails to explain why MR severity varies among individuals with similar degrees of tethering(9). Recent evidence showed that MV leaflets can enlarge in response to LV morphological changes(9-12), with the potential to reduce MR(10). Experimentally, mechanical stretch can promote adaptive MV growth(11), but little is known about the clinical implications of this phenomenon. A naturally occurring setting in which MV adaptation can be studied is in patients with chronic aortic regurgitation (AR), in whom functional MR is infrequent (13,14) despite often severe LV dilatation (6,8,13-21). This absence of MR challenges the concept linking functional MR solely to LV remodeling. Interestingly, necropsy data previously demonstrated MV enlargement in chronic AR(22), but this finding has not been related to functional MR or its determinants in vivo. Whether or not this phenomenon can be seen as an adaptation counterbalancing LV dilatation to prevent MR is unknown.

We tested the hypothesis that MV enlargement occurs in chronic AR and preserves normal mitral geometry relative to the dilated LV to prevent MR. We first assessed functional MR prevalence in chronic AR by database review. We then prospectively enrolled patients for three-dimensional (3D) echocardiography to assess MV size and its relation with LV geometry and function in patients with either chronic AR, functional MR (ischemic or non-ischemic) or normal controls using recently developed capabilities for measuring MV area noninvasively(10).

Methods

Retrospective analysis: To assess the prevalence of MR in patients with aortic regurgitation, we searched our institutional echocardiographic database for patients more than 18 years old with
moderate or severe AR who had a transthoracic echocardiogram within the last 5 years. Exclusion criteria were more than mild systolic dysfunction (LV ejection fraction < 40%), LV regional wall motion abnormality, severe aortic stenosis (valve area < 1.0 cm\(^2\)), mitral valve organic pathology (prolapse, rheumatic disease, mitral cleft, endocarditis and extensive annular calcification), presence of aortic or mitral prosthesis and Marfan disease. In all patients having more than mild MR, the echocardiographic images were reviewed to confirm the presence of functional MR.

**Prospective recruitment:** From January 2011 to June 2012, we prospectively enrolled 90 subjects for 3D echocardiography: 30 consecutive patients who had at least moderate AR without any previously stated exclusion criteria, 30 patients with moderate or severe functional MR (ischemic or non-ischemic) and LV end-diastolic dimension comparable to the AR group, and 30 normal controls (age and gender comparable to AR group) with normal echocardiograms and without known cardiac disease (patients with treated hypertension and no evident LV hypertrophy were not excluded). AR severity was assessed with an integrative approach using color Doppler (vena contracta), regurgitant volume and fraction, and assessment of flow reversal in the descending aorta (23). MR was graded as trace, mild, moderate or severe integrating color Doppler jet area and vena contracta width (23-25). Medical records were consulted to assess the cause and known duration of AR. All patients gave informed consent prior to enrollment. The study was approved by the hospital’s Institutional Review Board.

**Echocardiography:** All prospectively enrolled patients underwent standard transthoracic echocardiography using a Philips iE33 scanner with a 5-MHz transducer. Full volume 3D datasets were obtained from the apical window using an X3 matrix-array transducer. The analysis was performed by a single observer using QLAB 5.1 (Philips, Andover, MA) and
custom software for mitral valve area and tethering geometry (Omni4D, MD Handschumacher). The 3D datasets were analyzed separately and blinded to the presence and severity of AR and MR. 3D LV end-diastolic and end-systolic volumes were measured. LV sphericity was evaluated by the ratio of short-axis diameter / long-axis length at end-diastole and end-systole (8,26). Mid-systolic (identified by frame count) tethering distances from papillary muscle tips to contralateral annulus (26) were measured from the 3D dataset. Mid-systolic mitral annular area was calculated as the projection of the annular trace onto its average or least-squares plane. Total mitral leaflet area was measured in diastole (Figure 1) using a previously described and validated method that integrates valve area traced from the 3D dataset(10). Closure area was defined as the closed leaflet surface between LV and left atrium in mid-systole and thus represents the minimal area that needs to be covered by the leaflets in order to occlude the mitral orifice. The ratios of total leaflet to annular area, and total leaflet area to closure area were calculated to assess the adequacy of leaflet adaptation relative to LV and annular changes. Dimensions, areas and volumes were indexed for body surface area. Mitral valve thickness was measured on the 2D echo datasets in parasternal long-axis view in a diastolic frame without rapid motion with the leaflets as perpendicular as possible to the echocardiographic beam to take advantage of its axial resolution (27-29). As functional MR can be related to decreased closing forces in a failing ventricle (30,31), we also measured key parameters of LV contractility including 3D-calculated LVEF, end-systolic wall stress reflecting afterload(32,33), and end-systolic volume index, which is relatively preload-independent. In the absence of continuous wave Doppler in the patients without MR to provide true transmitral pressure, mitral closing forces were estimated as Force (Newton) = 0.0133 * systolic arterial pressure (mmHg) * leaflet area (cm²).

Statistics:
Continuous variables are expressed as mean±standard deviation and categorical variables as number (%). Differences in proportions were assessed by Chi-squared test. Logistic univariate and multivariate regressions were used to assess the predictors of significant MR in the database population. Age, gender, LVEF and LV end-diastolic and end-systolic dimensions were included in the model. In the prospectively recruited population, echocardiographic variables of the AR group were compared with those of the functional MR and control groups. Differences in means amongst three groups were assessed one-way analysis of variance (ANOVA) with Bonferroni multiple-comparison tests. We assessed the differential relation of mitral leaflet area and LV end-diastolic volume by linear regression including group (AR or functional MR) as an interaction term. Known AR duration and leaflet area in the AR group was also assessed with linear regressions. Leaflet thickness and area were compared between patients with AR jets that were central versus posteriorly directed onto the anterior mitral leaflet. Multivariate logistic regression was used to assess the relation of total leaflet to closure area ratio and the presence of MR, including in the model variables describing LV function that were significant between FMR and AR patients by univariate analysis: LVEF, end-systolic wall stress and end-systolic volume index. Regression coefficients standardized for standard deviation were computed. Statistical analysis was performed with Stata/IC 11.2 (StataCorp LP, Tx).

RESULTS

Retrospective review: We identified a total of 816 patients with moderate or severe AR (Table 1). Moderate or severe functional MR was found in 46 patients (5.6%). Age (p<0.01), LV ejection fraction (p<0.01), LV end-diastolic (p<0.01) and end-systolic dimensions (p<0.01) were significant predictors of MR. In multivariate analysis, age (p<0.01), gender (p<0.01) and LV end-diastolic dimension (p=0.02) were significant.
Prospective study: A total of 90 patients were enrolled (30 with AR, 30 with functional MR and 30 normal controls), with characteristics shown in Table 2. Causes of AR were endocarditis (5 cases, with infection resolved medically), congenital aortic valve disease (21 cases) and aortic root dilatation (4 cases), and the median known AR duration was 24 months (1 month to 10 years). The AR and control groups were not significantly different in age, gender, body surface area, or comorbidities (hypertension and diabetes); more of the AR patients were treated with renin-angiotensin system blockers for afterload reduction compared to controls (57% vs 27%, p=0.04). Only one patient in the AR group had more than mild (moderate to severe) MR, with LV enlargement, mild global dysfunction, and incomplete mitral leaflet closure. Functional MR patients were similar for gender, but older than control and AR patients. The functional MR group mostly consisted of ischemic cardiomyopathy (25 ischemic, 5 non-ischemic) and none of these patients had more than mild AR.

AR and functional MR patients had a comparable increase in LV volumes compared to controls (end-diastolic volume index: 82±22 vs 86±23 vs 51±12 cm$^3$/m$^2$ for AR, functional MR and control groups, p<0.01). Also, LV sphericity index, tethering distances, annulus area and closure area were all similarly increased in AR and functional MR groups compared to control patients. End-systolic wall stress was significantly increased in functional MR compared to AR and control patients, consistent with increased afterload, and comparable to the results of Reichek et al. (32). Mitral closing force was increased in both functional MR and AR groups compared to control patients, driven by increased leaflet and annular area. 3D MV closure area, annulus area and total leaflet area are displayed in Table 2 and Figure 2. Total mitral leaflet area was the largest in AR patients (31.3% larger than normal, 16.8±3.7 vs 12.8±2.3 cm$^2$ for controls, p<0.01), with comparable differences persisting when normalized to body surface area.
was a significant relation between valve size and AR regurgitant volume (p=0.01). While functional MR patients also had some degree of valve enlargement, the magnitude was significantly less than in AR patients (Table 2). The ratio of total leaflet area to systolic closure area was preserved in the AR group and identical to controls (1.4±0.2 in both groups, p=0.26), indicating adequate leaflet compensation for the increased area requirements demanded by the dilated LV. In contrast, this ratio was significantly decreased in functional MR patients (1.2±0.1, p<0.01 vs control and AR groups), indicating a relatively smaller valve in relation to the dilated LV and annulus. There was no significant relation between age and leaflet to closure area ratio in any studied group or the overall population (p=0.20). The ratio of total leaflet area to annulus area showed the same pattern (1.7±0.2 vs 1.5±0.2 vs 1.6±0.2 for AR, functional MR and controls, p<0.01 between AR and functional MR) with a preserved ratio in AR and a reduced one in functional MR patients. Patients with AR and functional MR also had increased mitral leaflet thickness compared to controls (2.4±0.3 vs 2.5±0.6 vs 2.1±0.4 mm for AR, functional MR and controls, p<0.01). An example of increased 3D leaflet area in a patient with severe AR and dilated LV but only trace MR vs a control subject with comparable age and body surface area is shown in Figure 3.

In both AR and functional MR groups, there was a significant linear relation between mitral valve leaflet area and LV end-diastolic volume. However, the magnitude of valve enlargement relative to LV size was greater in AR patients (Figure 4, p=0.004 between FMR and AR groups). 21/30 AR patients had the regurgitant jet posteriorly directed onto the anterior mitral leaflet, but without difference in mitral leaflet area or thickness when compared with those with central jets (leaflet area 8.8 vs 9.0 cm2/m2, p=0.86; anterior thickness 2.5±0.3 vs 2.4±0.5 mm, p=0.76). There was no effect of known AR time duration on the degree of mitral valve
enlargement (p=0.45). A subset of 5 patients had a history of aortic valve endocarditis and sudden onset of moderate to severe AR. These patients were not significantly different from other AR patients regarding LV volume and mitral valve leaflet area in the chronic compensated state studied by 3D echo.

Multivariate predictors of MR: Table 2 presents univariate comparison of means between AR, FMR and control groups. LVEF, end-systolic wall stress and end-systolic volume index were significantly different in AR compared with FMR groups, and these differences could affect MR severity. In a multivariate analysis controlling for those variables, the ratio of total leaflet/closure area remained significantly associated with the presence of MR (standardized regression coefficient of 0.07, p=0.029) along with LVEF (standardized regression coefficient of 0.04, p=0.025); end-systolic volume index and end-systolic wall stress had p values of 0.057 and 0.098, respectively.

Discussion

The results of this study show that despite an enlarged LV, increased sphericity, longer tethering distances and dilated mitral annulus, patients with chronic compensated AR have a surprisingly low incidence of functional MR. While the absence of MR is consistent with the usually slow clinical evolution of chronic compensated AR, this observation challenges the current concepts relating functional MR solely to LV remodeling. Three-dimensional reconstruction of the mitral valve showed that AR patients have a compensatory, greater than 30% increase in their mitral leaflet area, which remains proportional to the LV volume and the demands it imposes in terms of mitral systolic closure area. Interestingly, the AR group also had mildly thicker mitral leaflets, suggesting that enlargement is not due to passive stretch alone and raising the possibility of active growth of cells, matrix, or both. In contrast, patients with functional MR had a
proportionally smaller valve increase despite similar LV size, sphericity index and tethering
distances, suggesting possible factors that can limit or favor mitral valve growth depending on
the underlying pathophysiology. The ratio of total leaflet area to the area required for leaflet
closure, a strong determinant of MR(10), was also preserved in AR and reduced in functional
MR. Valve area also increased more steeply with increasing LV end-diastolic volume in AR
versus FMR. These results are in accordance with the necropsy data of Mautner et al.(22) that
showed increased mitral valve area and mass in AR, and add the observations of relatively lesser
increases in mitral valve area in functional MR, with a decreased ratio of total to closure leaflet
areas. Of note, the absolute valve areas obtained in our study are greater than those reported by
necropsy, which may relate to different measurement methods: in the necropsy study, the leaflets
were formalin-fixed and excised 2 to 3 mm caudal to the annulus, which, spread over the entire
annulus, can make a substantial difference in total area. The relative increase in area compared
to controls was similar in both studies.

These results add to the growing literature suggesting that valve leaflets are able to
remodel and adapt in response to LV morphological changes, rather than being only passive
flaps. Interestingly, increased aortic leaflets dimensions have also been reported in patients with
AR and aortic root dilation, suggesting aortic valve adaptation(34). Insights from recent animal
studies suggest that mitral valve mechanical stretch can induce valve growth(11) by reactivating
embryonic development pathways, also shown with mechanical stretch of in vitro valve
constructs(35). Of note, the same in vivo study showed significant valve enlargement after only
60 days of mechanical stretch. That is consistent with our subset of patients having shorter AR
evolution but the same degree of valve enlargement in the chronic state of LV dilatation. While
mechanical stretch is likely involved, other potential mechanisms may also stimulate valve
growth. It has been shown that LV eccentric hypertrophy in AR is the result of numerous extracellular matrix genes being modulated in the myocardium(36), and expression of these genes is also modified in MR-induced volume overload(37). It is possible that mitral valve tissue shares some of these molecular remodeling mechanisms present in the LV myocardium, which could promote valve enlargement in parallel with LV dilatation. Interestingly, a previous animal study of LV pressure overload was associated with not only mitral but also tricuspid valve changes, leading the authors to suggest the possibility of circulating factors inducing valve remodeling (38).

**Implication for functional MR:** We demonstrate here that the compensated chronic AR population shows adequate mitral leaflet adaptation, even with severe LV dilatation. In addition to disturbed ventricular geometry, functional MR is the result of an imbalance between closing and tethering forces (30,31). Importantly, a larger valve and annulus not only provide more tissue to cover the increased closure area, but also contribute to greater closing forces (proportional to area). In the multivariate analysis, the leaflet to closure area ratio was a strong predictor of functional MR, independent of LVEF, systolic wall stress and LV end-systolic volume index. Decreased LVEF, which reflects the underlying cardiac pathology but also the additional remodeling imposed by the presence of MR, was also significant. The presence of MR therefore depends on both leaflet enlargement and LV contractility. This adaptation is however inadequate in patients with functional MR (less valve enlargement despite comparable LV size), which remains common in ischemic and myopathic heart failure. It will therefore be relevant in future work to consider factors that can potentially impair leaflet growth in these patients. Interestingly, while valve enlargement can promote mitral coaptation, other results have suggested that leaflet remodeling can potentially induce maladaptive valve stiffness and
fibrosis(39), interfering with valve function (40,41). This suggests that mitral leaflet remodeling could be a double-edged sword, preventing MR in certain situations, but with the potential of contributing to MR in other cases. One major difference between our chronic stable AR population and other ischemic or non-ischemic cardiomyopathies is the preserved systolic function and the absence of clinical heart failure. Heart failure is associated with strong humoral and pro-inflammatory cytokine activation, factors well known to induce and modify remodeling in the LV and numerous other organs. Although renin-angiotensin and adrenergic systems are also activated in chronic AR (42,43), the magnitude of this activation in asymptomatic patients with preserved function is likely lower than what is seen in the setting of ischemic and non-ischemic systolic dysfunction. It is currently unknown if this exaggerated humoral activation can modify valve leaflet growth, although the pro-fibrotic effects of angiotensin are well described (44,45). Future mechanistic studies are warranted to explore the factors potentially limiting leaflet growth and flexible closure, as they could eventually represent future therapeutic targets.

Limitations: The observed increases in leaflet area and thickness suggest possible cellular growth activation, but no biological samples were available in this imaging study. Our study shows that compensated AR is associated with adequate mitral valve adaptation; but the biological mechanisms leading to valve growth need to be explored. We are currently planning additional studies looking at valve area over time in chronic AR, acute AR, and the transition to decompensated heart failure, where clinical experience indicates FMR is more common. Also, the influence of other variables such as age, medication and comorbidities on mitral valve adaptation and incidence of FMR in various populations (ischemic and non-ischemic heart failure) needs to be assessed in clinical studies designed to address those influences.
Conclusion: Patients with chronic, clinically stable moderate to severe aortic regurgitation have a large increase in mitral leaflet size. This increase is proportional to the LV enlargement and, in addition to preserved contractility, can represent an adaptative mechanism to prevent mitral regurgitation in a dilated ventricle. Further mechanistic studies are needed to explore how we can modulate this adaptation to prevent functional MR in other diseases.
REFERENCES:


7. Otsuji Y, Handschumacher MD, Schwammenthal E et al. Insights From Three-Dimensional Echocardiography Into the Mechanism of Functional Mitral Regurgitation:


Figures legends:

**Figure 1: Mitral valve reconstruction for total leaflet area measurement using three-dimensional echocardiography.**
Sequential leaflet tracing in multiple planes allows computation of total mitral leaflet area (measurable clearly only in diastole, because the systolic areas of leaflet coaptation cannot be uniformly visualized (10)).

**Figure 2: Total leaflet area, mid-systolic closure and annulus areas in control, functional mitral regurgitation and aortic regurgitation patients.**
The mid-systolic closure and annulus areas are both similarly increased in AR and functional MR patients compared to controls. In AR, there is a proportional increase in total valve area, maintaining a normal relation between valve and left ventricle sizes, which is not the case in patients with functional MR.

**Figure 3: Mitral valve enlargement in aortic regurgitation: example.**
Representative example showing three-dimensional reconstructions of a normal and chronic aortic regurgitation patients. Top row: Transthoracic echocardiogram showing severe aortic regurgitation (A), dilated left ventricle at 6.8 cm (B) and only trace mitral regurgitation (C). Middle row: Different projections of a 3D reconstruction of the mitral leaflets showing increased annulus size and larger leaflet area. Bottom row: Same reconstruction in a control patient matched for age and body surface area.

**Figure 4: Relation between total leaflet area and left ventricular volume in aortic regurgitation and patients with functional mitral regurgitation.**
In both groups, there is a linear relation between mitral valve size and left ventricular volume. The increase in valve size is however greater in patients with AR compared to those with functional MR.
### Table 1: Echocardiographic characteristics of moderate to severe AR patients

<table>
<thead>
<tr>
<th></th>
<th>All population (n = 816)</th>
<th>MR (n = 46)</th>
<th>No MR (n = 770)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64 ± 18</td>
<td>72 ± 14</td>
<td>63 ± 18</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Number of Male</td>
<td>499 (61)</td>
<td>22 (48)</td>
<td>477 (62)</td>
<td>0.06</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>64 ± 9</td>
<td>61 ± 11</td>
<td>65 ± 8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVIDed (mm)</td>
<td>49 ± 8</td>
<td>52 ± 8</td>
<td>49 ± 8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVIDes (mm)</td>
<td>32 ± 7</td>
<td>36 ± 8</td>
<td>32 ± 7</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

LVEF: Left ventricular ejection fraction; LVIDed: Left ventricle internal diameter at end-diastole; LVIDes: Left ventricle internal diameter at end-systole.
### Table 2: Echocardiographic characteristics of aortic regurgitation, functional mitral regurgitation and control patients

<table>
<thead>
<tr>
<th></th>
<th>AR</th>
<th>Normal</th>
<th>FMR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=30</td>
<td>n=30</td>
<td>n=30</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>47±17†</td>
<td>45±17</td>
<td>69±14*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gender (number of male)</td>
<td>22 (73)</td>
<td>15 (50)</td>
<td>18 (60)</td>
<td>0.20</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.9±0.2</td>
<td>1.8±0.2</td>
<td>1.9±0.2</td>
<td>0.06</td>
</tr>
<tr>
<td>MR more than mild</td>
<td>1 (3%)</td>
<td>0 (0)</td>
<td>30 (100)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEDV (cm³)</td>
<td>154±46*</td>
<td>92±23</td>
<td>167±52*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEDV index (cm³/m²)</td>
<td>82±22*</td>
<td>51±12</td>
<td>86±23*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVESV (cm³)</td>
<td>62±25*†</td>
<td>33±12</td>
<td>106±44*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVESV index (cm³/m²)</td>
<td>33±13*†</td>
<td>18±7</td>
<td>55±20*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>61±7†</td>
<td>64±7</td>
<td>37±11*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sphericity ratio (D/L), diastole</td>
<td>0.52±0.07</td>
<td>0.44±0.05</td>
<td>0.52±0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sphericity ratio (D/L), systole</td>
<td>0.44±0.06</td>
<td>0.36±0.07</td>
<td>0.47±0.06</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-systolic tethering distance, medial PM (mm)</td>
<td>43±7*</td>
<td>38±4</td>
<td>41±6</td>
<td>&lt;0.01</td>
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<tr>
<td>Mid-systolic tethering distance, lateral PM (mm)</td>
<td>42±7*</td>
<td>36±5</td>
<td>39±5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Leaflet area (cm²)</td>
<td>16.8±3.7*</td>
<td>12.8±2.3</td>
<td>15.4±2.7*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Control Group</td>
<td>FMR Group</td>
<td>FMR vs Control</td>
<td>p Value</td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------------</td>
<td>-----------</td>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td>Leaflet area index (cm²/m²)</td>
<td>8.9±1.6*†</td>
<td>7.1±1.3</td>
<td>8.0±1.4</td>
<td>&lt;0.01</td>
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<tr>
<td>Mid-systolic closure area (cm²)</td>
<td>12.1±2.8*</td>
<td>9.7±1.9</td>
<td>12.6±2.0*</td>
<td>&lt;0.01</td>
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<tr>
<td>Mid-systolic annulus area (cm²)</td>
<td>9.9±2.2*</td>
<td>8.2±1.6</td>
<td>10.0±1.5*</td>
<td>&lt;0.01</td>
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<tr>
<td>Leaflet area/Closure area ratio</td>
<td>1.4±0.2†</td>
<td>1.4±0.2</td>
<td>1.2±0.1*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Leaflet area/annulus area ratio</td>
<td>1.7±0.2†</td>
<td>1.6±0.2</td>
<td>1.5±0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>End systolic wall stress (X10³ dyn/cm²)</td>
<td>83±23†</td>
<td>71±23</td>
<td>135±48*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Closing forces (N)</td>
<td>28.0±8.6*</td>
<td>20.3±3.9</td>
<td>25.3±6.1*</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

AR: Aortic regurgitation; FMR: Functional mitral regurgitation; LVIDed: Left ventricle internal diameter at end-diastole; LVIDes: Left ventricle internal diameter and end-systole. LVEDV: Left ventricle end-diastolic volume; LVESV: Left ventricle end-systolic volume; LVEF: Left ventricular ejection fraction; PM: Papillary muscle. D: Left ventricle short axis diameter; L: Left ventricle long axis dimension; N: Newton.

*: p<0.05 vs control group

†: p<0.05 vs FMR group
**AI patient**

- Annulus area: 11.9 cm²
- Leaflet area: 22.3 cm²

**Control patient**

- Annulus area: 8.8 cm²
- Leaflet area: 14.5 cm²
Total mitral valve leaflet area vs LV end-diastolic volume in aortic regurgitation and functional MR patients

AR: $y = 0.067x + 6.3053$

FMR: $y = 0.0242x + 11.096$

$p = 0.004$