Novel Mechanistic Insights Into Atrial Functional Mitral Regurgitation – 3-Dimensional Echocardiographic Study –

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Background: Left atrial remodeling caused by persistent atrial fibrillation (AF) causes atrial functional mitral regurgitation (MR), even though left ventricular (LV) remodeling and organic changes of the mitral leaflets are lacking. The detailed mechanism of atrial functional MR has not been fully investigated.

Methods and Results: Of 1,167 patients with AF who underwent 3D transesophageal echocardiography, 75 patients were retrospectively selected who developed no, mild, or moderate-to-severe atrial functional MR (n=25 in each group) despite an LV ejection fraction ≥50% and LV volumes within the normal range. Mitral valve morphology and dynamics were analyzed. Patients with moderate-to-severe MR had a larger mitral annulus (MA) area, smaller MA area fraction, and greater nonplanarity angle and tethering angle of the posterior mitral leaflet (PML) compared with other groups (all P<0.001). In the multiple regression analysis, the MA area, MA area fraction, nonplanarity angle, and PML angle were independent determinants of the effective regurgitant orifice area of MR after adjusting for LV parameters (adjusted R²=0.725, P<0.001). The PML angle and MA area had a higher standardized regression coefficient (β=0.403, P<0.001, β=0.404, P<0.001, respectively) than the other variables.

Conclusions: Functional atrial MR in persistent AF is caused by not only MA dilatation, but also by multiple factors including the MA contractile dysfunction, disruption of the annular saddle shape, and atriogenic PML tethering. (Circ J 2016; 80: 2240–2248)

Key Words: Atrial fibrillation; Left atrium; Mitral regurgitation; Three-dimensional transesophageal echocardiography

The long burden of persistent atrial fibrillation (AF) leads to progression of left atrial (LA) remodeling.1,2 A severely enlarged LA sometimes causes significant functional mitral regurgitation (MR), though there is no evidence of left ventricular (LV) remodeling or organic changes of the mitral valve (MV). Such MR seen in patients with AF was recently termed “atrial functional MR”.3–5 The interference of the coaptation of the leaflets because of mitral annular (MA) dilatation has been postulated as the main worsening factor of atrial MR.4,6,7 However, this postulation has been controversial8 and the 3-dimensional (3D) investigation of the mechanism of atrial functional MR is still limited.4 In patients with lone AF, significant MR may not be so rare4,9 and has been an important therapeutic target4,7 because of the association with a poor prognosis.10 Recent development of medical devices has provided various treatment options ranging from surgical MV repair to catheter-based annuloplasty or leaflet clipping for MR.11–13 To decide the most effective therapeutic strategy for the MV, understanding the precise mechanism of the atrial functional MR is essential. The utility of 3D transesophageal echocardiography (TEE) for evaluating the detailed pathogenesis of MR has been widely accepted.14,15 Accordingly, the present study aimed to investigate the characteristics of the MV structure and dynamics through 3D-TEE in patients with atrial functional MR and lone persistent AF.

Study Protocol

The subjects were enrolled into the present study as illustrated in Figure 1. Definitions of atrial functional MR were as follows: MR that occurs with LA enlargement, and is not caused

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The LV volumes and LVEF were calculated by a modified Simpson’s method. The LA volume was defined as the largest LA volume just before the MV opening. It was measured from the apical view with the biplane method of disks and indexed to the body surface area. The right atrial (RA) area was measured on a still image of the apical 4-chamber view at mid-systole. The peak velocity of the early (E) transmitral flow was recorded from the long-axis view by pulsed Doppler echocardiography. Tissue Doppler imaging was used to measure the early peak diastolic velocity (E’) at the mitral annular septal and lateral corners. The E/E’ ratio was calculated as E divided by the average of the 2 E’ velocities. We averaged 3 consecutive beats in SR and 5 consecutive beats in AF to obtain these measurements.

Color-flow Doppler images of the MR and tricuspid regurgitation (TR) jets were acquired at a Nyquist limit of 50–60 cm/s. Quantification of the MR was performed as recommended by the American Society of Echocardiography using an integrated method, including measurement of the vena contracta width, effective regurgitant orifice area (EROA), and the area ratio of the MR jet to LA in mid-systole. The vena contracta width was measured from a magnified parasternal long-axis view. The EROA was calculated using the proximal isovelocity surface area method from apical views. The area ratio of the MR jet to LA was averaged from the apical 4- and 2-chamber views. Moderate-to-severe MR was defined by the presence of at least 2 of 3 color Doppler criteria categorizing the MR severity (ratio of the MR jet area to the LA area ≥20%, vena contracta width ≥3 mm, EROA ≥0.3 cm²). Mild MR was defined by the presence of at least 2 of 3 criteria (ratio of the MR jet area to the LA area <20%, vena contracta width <3 mm, EROA <0.3 cm²). Trace MR was classified as no MR.

Conventional TTE Examination

The 2D images were recorded with an IE33 ultrasound system equipped with an SS-1 phased array transducer (Philips Medical Systems, Andover, MA, USA). Each echocardiographic parameter was determined based on the American Society of Echocardiography recommendations.17,18 The LV volumes and LVEF were calculated by a modified Simpson’s method. The LA volume was defined as the largest LA volume just before the MV opening. It was measured from the apical view with the biplane method of disks and indexed to the body surface area. The right atrial (RA) area was measured on a still image of the apical 4-chamber view at mid-systole. The peak velocity of the early (E) transmitral flow was recorded from the long-axis view by pulsed Doppler echocardiography. Tissue Doppler imaging was used to measure the early peak diastolic velocity (E’) at the mitral annular septal and lateral corners. The E/E’ ratio was calculated as E divided by the average of the 2 E’ velocities. We averaged 3 consecutive beats in SR and 5 consecutive beats in AF to obtain these measurements.

Color-flow Doppler images of the MR and tricuspid regurgitation (TR) jets were acquired at a Nyquist limit of 50–60 cm/s. Quantification of the MR was performed as recommended by the American Society of Echocardiography using an integrated method, including measurement of the vena contracta width, effective regurgitant orifice area (EROA), and the area ratio of the MR jet to LA in mid-systole. The vena contracta width was measured from a magnified parasternal long-axis view. The EROA was calculated using the proximal isovelocity surface area method from apical views. The area ratio of the MR jet to LA was averaged from the apical 4- and 2-chamber views. Moderate-to-severe MR was defined by the presence of at least 2 of 3 color Doppler criteria categorizing the MR severity (ratio of the MR jet area to the LA area ≥20%, vena contracta width ≥3 mm, EROA ≥0.3 cm²). Mild MR was defined by the presence of at least 2 of 3 criteria (ratio of the MR jet area to the LA area <20%, vena contracta width <3 mm, EROA <0.3 cm²). Trace MR was classified as no MR. The ratio of the maximal TR jet area on color-flow mapping...
to RA area was measured on the apical 4-chamber view, as previously described.20

3D TEE Examination
After an oral viscous and spray lidocaine gargle and swallow for local pharyngeal and esophageal anesthesia, all patients received intravenous sedation. TEE was performed using the iE33 ultrasound system equipped with an X7-2t TEE ultrasound probe providing a range frequency of 2.0–7.0MHz and both 2D and 3D matrix arrays (Philips Medical Systems). In the 25 control subjects, the 3D images were recorded with R-wave gating over 4 beats. In the 75 patients with AF, a 3D live zoom mode of an index beat, which was the beat after the nearly equal preceding and pre-preceding intervals, was used for each measurement as previously described.21 To increase the temporal resolution, care was taken to minimize the sector width and length, and the 3D images were recorded at a frame rate of at least 9 frames/s.

Dynamic MV Geometric Analysis
The 3D datasets were analyzed using the 3D, knowledge-based, eSie Valves valve-modeling software, (Siemens Medical Solutions, Mountain View, CA, USA). The feasibility and methodology of the dynamic geometric analysis has been established previously.22,23 Briefly, after importing the data into the software, the end-systolic and end-diastolic frames were decided by visual identification. Next, the MV annulus and leaflets were automatically detected over each frame to construct a detailed morphology of the MV. After manual correction of all alignments of the MV in each frame by the observer, the 3D MV model and quantified MV morphological measurements were displayed (Figure 2). Measured data were exported for a statistical analysis per frame and per percentage of the cardiac cycle. Using this software, we automatically quantified the following measurements: MA anterior-posterior diameter, MA anterolateral-posteromedial diameter, sphericity index, as the ratio between anterior-posterior and anterolateral-posteromedial diameters, MA circumference, 2D (projected) MA area, nonplanarity angle (NPA) of the annulus, quantification of the “saddle shape” of the annulus, MV tenting volume, and anterior mitral leaflet (AML) and posterior mitral leaflet (PML) areas. The ratio of the PML area to the AML area was calculated. The sum of both leaflet closure areas, defined as the total closure area and the ratio of the total leaflet closure area to the annulus area, was calculated. The systolic annulus area fraction was defined as (MA area late systole–MA area early systole)/MA area late systole×100%) as previously described.5 Because the measurement of the leaflet tethering angles is not supported by eSie Valves, we determined them in the mid-systole frame using the 3D quantification of QLAB (Philips Ultrasound) as described previously (Figure 2).24

Statistical Analysis
Data are summarized as the mean±standard deviation for continuous variables. Categorical variables are presented as percentages. The intergroup comparisons of the baseline characteristics, measurements of the echocardiography at specific time points in the cardiac cycle, and intragroup comparisons of the MA area and NPA during the cardiac cycle used 1-way ANOVA with post-hoc Tukey test. The linear association between the continuous variables was made using Pearson’s correlation coefficient. Regression analysis was used to evaluate the association between the MV measurements and EROA. A multivariate linear regression was further performed among
Baseline Characteristics and TTE Findings

The general characteristics of the studied patients are summarized in Table 1. The patients with moderate-to-severe atrial MR had longer AF duration compared with the lesser MR groups. Regression analysis revealed significant correlation between AF duration and EROA ($r=0.645, P<0.001$). The TTE measurements and their correlations with EROA are shown in Table 2. Notably, the LAVI displayed the strongest correlation with EROA. There was also significant correlation among the variables with $P$ values of $<0.10$ by a univariate correlation analysis to identify the independent determinants of EROA. To evaluate the correlation between the other variables, we performed a collinearity analysis before the multivariate analysis. To avoid any problems caused by the collinearity, only the annulus area was entered into the multivariate models instead of the measurements of the annulus diameter and leaflet area. The reproducibility was tested in 15 randomly selected patients. A value of $P<0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS statistics 22 software (SPSS Inc, Chicago, IL, USA).

### Results

#### Baseline Characteristics and TTE Findings

The general characteristics of the studied patients are summarized in Table 1. The patients with moderate-to-severe atrial MR had longer AF duration compared with the lesser MR groups. Regression analysis revealed significant correlation between AF duration and EROA ($r=0.645, P<0.001$). The TTE measurements and their correlations with EROA are shown in Table 2. Notably, the LAVI displayed the strongest correlation with EROA. There was also significant correlation among the variables with $P$ values of $<0.10$ by a univariate correlation analysis to identify the independent determinants of EROA. To evaluate the correlation between the other variables, we performed a collinearity analysis before the multivariate analysis. To avoid any problems caused by the collinearity, only the annulus area was entered into the multivariate models instead of the measurements of the annulus diameter and leaflet area. The reproducibility was tested in 15 randomly selected patients. A value of $P<0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS statistics 22 software (SPSS Inc, Chicago, IL, USA).
Table 3. Comparison of the 3D Mitral Valvular Geometry of the Controls and Patients With AF in a Study of Atrial Functional MR

<table>
<thead>
<tr>
<th></th>
<th>Control (n=25)</th>
<th>No MR (n=25)</th>
<th>Mild MR (n=25)</th>
<th>Moderate-to-severe MR (n=25)</th>
<th>P value*</th>
<th>r</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mitral annulus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anteroposterior diameter, cm</td>
<td>2.99±0.37†</td>
<td>3.11±0.34†</td>
<td>3.31±0.40†</td>
<td>3.74±0.66</td>
<td>&lt;0.001</td>
<td>0.559</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anterolateral-posteromedial diameter, cm</td>
<td>3.37±0.44‡</td>
<td>3.44±0.37†</td>
<td>3.71±0.39†</td>
<td>4.08±0.62</td>
<td>&lt;0.001</td>
<td>0.551</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sphericity index</td>
<td>0.89±0.06</td>
<td>0.90±0.07</td>
<td>0.90±0.11</td>
<td>0.92±0.09</td>
<td>0.792</td>
<td>0.076</td>
<td>0.445</td>
</tr>
<tr>
<td>Circumference, cm</td>
<td>10.45±1.22‡</td>
<td>10.69±1.01†</td>
<td>11.68±1.22†</td>
<td>12.79±1.87</td>
<td>&lt;0.001</td>
<td>0.564</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Annulus area, cm²</td>
<td>7.76±1.56†</td>
<td>8.59±1.65†</td>
<td>9.71±1.94†</td>
<td>12.34±3.18</td>
<td>&lt;0.001</td>
<td>0.640</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic annulus area fraction, %</td>
<td>22.35±1.04</td>
<td>15.57±7.52‡</td>
<td>11.04±7.52‡</td>
<td>6.87±4.49</td>
<td>&lt;0.001</td>
<td>−0.413</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonplanarity angle, °</td>
<td>151±7†</td>
<td>151±8†</td>
<td>152±11†</td>
<td>162±7</td>
<td>&lt;0.001</td>
<td>0.529</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Mitral leaflets</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML angle, °</td>
<td>18±5</td>
<td>19±10†</td>
<td>18±5</td>
<td>15±3</td>
<td>0.012</td>
<td>−0.257</td>
<td>0.006</td>
</tr>
<tr>
<td>PML angle, °</td>
<td>29±11†</td>
<td>30±9†</td>
<td>31±8†</td>
<td>52±14</td>
<td>&lt;0.001</td>
<td>0.639</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AML area, cm²</td>
<td>4.62±0.85†</td>
<td>5.49±0.99†</td>
<td>6.07±1.42†</td>
<td>7.92±2.71</td>
<td>0.001</td>
<td>0.516</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PML area, cm²</td>
<td>3.99±1.09§</td>
<td>4.68±1.10†</td>
<td>5.34±1.34</td>
<td>5.11±1.08</td>
<td>0.001</td>
<td>0.197</td>
<td>0.049</td>
</tr>
<tr>
<td>PML to AML area ratio</td>
<td>0.86±0.22</td>
<td>0.85±0.17†</td>
<td>0.88±0.23†</td>
<td>0.65±0.17</td>
<td>&lt;0.001</td>
<td>−0.382</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total leaflet closure area, cm²</td>
<td>9.65±1.64†</td>
<td>10.17±1.85†</td>
<td>11.42±2.21†</td>
<td>13.06±3.45</td>
<td>&lt;0.001</td>
<td>0.314</td>
<td>0.003</td>
</tr>
<tr>
<td>Leaflet closure area to annulus area ratio</td>
<td>1.17±0.14</td>
<td>1.15±0.09‡</td>
<td>1.15±0.06‡</td>
<td>1.05±0.10</td>
<td>0.018</td>
<td>−0.379</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tenting volume, ml</td>
<td>1.46±0.62</td>
<td>1.54±0.74</td>
<td>2.12±1.08</td>
<td>1.72±0.86</td>
<td>0.316</td>
<td>0.049</td>
<td>0.620</td>
</tr>
</tbody>
</table>

Results are shown as the mean ± SD. *Statistical difference among the 4 groups. All measurements except the systolic annulus area fraction were the values measured during mid-systole. †P<0.01, ‡P<0.05 vs. patients with moderate-to-severe MR; §P<0.01 vs. patients with mild MR. AML, anterior mitral leaflet; NPA, nonplanarity angle; PML, posterior mitral leaflet. Other abbreviations as in Table 1.

Figure 3. Differences in the mitral valve (MV) morphology between mild and severe atrial functional mitral regurgitation (MR) in patients with persistent atrial fibrillation (AF). (A) Example of mild atrial MR: No tethering and normal coaptation of the leaflets are seen on 2D echocardiography (2DE). The 4D MV model shows a normal saddle-shaped annulus and preserved mitral annulus (MA) contraction during systole. (B) Example of severe atrial functional MR caused by AF lasting for 15 years. On 2DE, a huge left atrium (LA) causes mounting of the posterior MA on the bended posterior inlet of the left ventricle and results in posterior mitral leaflet (PML) dominant tethering (yellow arrow). The 4D MV model also reveals annular flattening, PML tethering displayed as blue, and a reduction of the free margin of the PML (red arrows). Please note the different Y-axis scales of the measurements of the annulus area. AML, anterior mitral leaflet; ED, end-diastole; ES, end-systole; LAVI, left atrial volume index.
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between the LAVI and duration of AF (P=0.590, P<0.001). LV size and EF were within the normal ranges and there were no correlations with LV parameters and EROA. The RA area, TR jet area and the ratio of the TR area to the RA area were greater in the moderate-to-severe MR group than in other groups. The mitral E velocity, MA E’ velocity and the E/E’ ratio tended to be higher in parallel with deterioration of MR.

**MV Parameters of 3D-TEE**

MV parameters measured by 3D-TEE were summarized in Table 3. The MA had a trend towards being larger and flatter and having worse contraction in the moderate-to-severe MR group than in other groups. The mitral E velocity, MA E’ velocity and the E/E’ ratio tended to be higher in parallel with deterioration of MR.

**Figure 4.** Differences in the 3D mitral annulus (MA) dynamics among the patients with atrial fibrillation (AF) and the controls. Measurements of MA area (A) and nonplanarity angle (B) in each phase of the cardiac cycle in patients with AF classified according to mitral regurgitation (MR) severity and control subjects. Intergroup comparisons at each time point revealed the moderate-to-severe atrial MR group showed the greatest values in both measurements (P<0.01 for both). Intragroup comparisons revealed that control subjects show a change in annulus morphology during the cardiac cycle (P<0.05 for both), whereas patients with AF show inadequate mitral annular contraction and saddle deepening in early systole. *P<0.01 compared with the other 3 groups at specific time points in the cardiac cycle (post-hoc test); †P<0.05 compared with values in other cardiac phases in the control group (post-hoc test).

**Figure 3** demonstrates the 3D-TEE findings of representative cases. In a patient with severe atrial MR, a huge LA causes the mounting of the posterior MA to the bended posterior inlet of the LV. Consequently, PML dominant tethering and restriction of PML margin occurred. Also, the patient with severe atrial MR demonstrated notable alterations of the annulus such as dilatation and flattening in comparison with patients showing mild atrial MR. The 4D analysis of MA dynamics showed that the extremely dilated annulus in the patient with severe atrial MR scarcely changed its area during the cardiac cycle and annulus contraction shown as systolic MA area fraction reduced compared with mild atrial MR.

**Table 4. Multivariate Regression Analysis of the Determinants Associated With EROA**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model using the MV variables (adjusted R²=0.726)</th>
<th>Model adjusted for the LA volume (adjusted R²=0.736)</th>
<th>Model adjusted for the LV variables (adjusted R²=0.725)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>P value</td>
<td>β</td>
</tr>
<tr>
<td>Annulus area, cm²</td>
<td>0.363</td>
<td>&lt;0.001</td>
<td>0.279</td>
</tr>
<tr>
<td>Annulus area fraction, %</td>
<td>−0.161</td>
<td>0.007</td>
<td>−0.151</td>
</tr>
<tr>
<td>Nonplanarity angle, °</td>
<td>0.177</td>
<td>0.008</td>
<td>0.179</td>
</tr>
<tr>
<td>AML angle, °</td>
<td>−0.144</td>
<td>0.042</td>
<td>−0.112</td>
</tr>
<tr>
<td>PML angle, °</td>
<td>0.351</td>
<td>&lt;0.001</td>
<td>0.324</td>
</tr>
<tr>
<td>PML to AML area ratio</td>
<td>−0.143</td>
<td>0.016</td>
<td>−0.109</td>
</tr>
<tr>
<td>Leaflet closure area to annulus area ratio</td>
<td>−0.020</td>
<td>0.738</td>
<td>−0.014</td>
</tr>
<tr>
<td>LA volume index, ml/m²</td>
<td>− −</td>
<td>− −</td>
<td>0.247</td>
</tr>
<tr>
<td>LV end-diastolic volume, ml/m²</td>
<td>− −</td>
<td>− −</td>
<td>− −</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>− −</td>
<td>− −</td>
<td>− −</td>
</tr>
<tr>
<td>Systolic arterial pressure, mmHg</td>
<td>0.068</td>
<td>0.220</td>
<td>0.054</td>
</tr>
</tbody>
</table>

β, standardized regression coefficient. Other abbreviations as in Tables 1–3.
Comparisons of Annular Dynamics

Differences of MA dynamics during end-diastole to end-systole in each group are shown in Figure 4. MA area and NPA were larger at all individual time points in patients with moderate-to-severe MR than in others. In the control subjects, MA area reduced consistent with annular contraction and NPA representing saddle-shape deepened markedly in early systole.

Determinants of Severity of Atrial Functional MR

The independent determinants of EROA were analyzed using multiple linear regression analysis (Table 4). MA area, annulus area fraction, NPA, and PML tethering angle were identified as having a primary independent contribution after adjusting for LVEDV and systolic arterial pressure. Also, these variables were significant predictors after adjusting for LAVI. It is noteworthy that the PML tethering angle and MA area achieved higher standardized regression coefficients compared with the other variables.

Reproducibility of the MV Parameters

Intraobserver correlation coefficients and mean absolute percentage errors for MA area, MA area fraction, NPA and PML angle were 0.98 and 6.2±5.0%, 0.91 and 5.9±4.2%, 0.95 and 3.2±2.0%, and 0.92 and 5.1±3.7%, respectively. Interobserver correlation coefficients and mean absolute percentage errors for the same parameters were 0.93 and 6.5±6.7%, 0.89 and 9.9±6.8%, 0.93 and 4.2±3.4%, and 0.91 and 9.5±4.5%, respectively.

Discussion

This study demonstrated that: (1) long-lasting AF causes LA remodeling that leads to morphological and functional changes in the MA and leaflets; (2) atrial functional MR has multiple deterioration factors including MA dilatation, a flattened annular saddle shape, annulus contractile dysfunction, and PML dominant tethering; and (3) the PML tethering angle is the most influential, independent factor for determining the EROA, along with annulus dilatation.

For a long time, whether MA dilatation alone is sufficient for the development of functional atrial MR has been controversial because there have been discrepant findings.3,5-8,27 Our findings provide novel evidence regarding this issue. Patients with AF had a trend of MA enlargement compared with the control subjects; however, that did not always lead to significant MR, which may be partly explained by compensatory enlargement of the leaflets, so-called mitral adaptation. Mitral adaptation has been observed in patients with LV remodeling and MA dilatation in ischemic or dilated cardiomyopathy.28 Although whether MA remodeling caused by AF-induced LA dilatation is also capable of such compensation has not been clarified thus far,26 our results showed that the mitral leaflets demonstrated the capacity of adaptation by compensatory enlargement to some extent in response to mechanical stretch from MA dilatation caused by the LA remodeling. However, the leaflets were unable to cover the extremely enlarged MA completely, as seen in the decrease of the leaflet closure area to annulus area ratio in the patients with moderate-to-severe MR. Thus, if MA dilates beyond the limits of leaflet adaptation, sufficient leaflet coaptation is impaired and atrial MR may occur.

Further, the most significant point we proved is that PML tethering unrelated to LV remodeling is seen in an enlarged LA and independently determines the severity of the atrial MR. Our results showed that the PML tethering angle became larger and the area ratio of the PML to the AML became smaller according to worsening MR. This finding may be supported by the recently proposed concept of “atriogenic PML tethering”.27 The extremely stretched LA posterior wall leads to inward bending of the posterobasal wall of the LV.28 The ventricular surface of the PML becomes pressed against the crest of the LV inlet, and the free margin of the PML available for coaptation decreases. Also, traction of the LA wall causes posterior annulus displacement onto the crest of the LV inlet, because the MA is histologically embedded in the LA wall.27 These morphological changes of the annulus augment the PML restriction via a mechanism in which LV remodeling does not contribute to it.27 Atriogenic PML tethering is practically observed in patients who undergo an MV repair for atrial functional MR,4 however, to the best of our knowledge, we have provided, for the first time with statistical significance, evidence of the importance of atriogenic PML tethering associated with aggravation of the functional atrial MR. The tenting volume has been considered a measure of the degree of leaflet tethering below the annular plane in functional MR related to LV remodeling.29 However, we found no correlation between the tenting volume and EROA in the present study, which may be explained by both the asymmetric pattern of the leaflet tethering and the flattened annulus.30

Other coexisting annular factors, such as the systolic circumferential contraction supporting effective leaflet coaptation and nonplanar geometry attenuating the leaflet stress, are also important for preventing regurgitation in a coordinated manner.30 The present study also revealed that annulus flattening and contractile dysfunction progressed in parallel with severe enlargement of the LA and MA and they significantly exerted an influence on the worsening of atrial MR. Regarding the other TTE findings, the RA and TR jet areas were greater in the moderate-to-severe MR group in comparison with the other groups. Long-standing AF can cause significant dilatation of not only the LA but also the RA, leading to mitral and tricuspid annular dilatation and causing valvular regurgitation.30 Dilatation and overload of the right-sided heart may interfere with the MA structure and dynamics; however, further research is required to confirm that. In the present study, E velocity, E’ velocity and E/E’ ratio tended to be higher in parallel with deterioration of MR. Interpretation of E’ and E/E’ ratio as markers of diastolic dysfunction has a limitation, especially in patients with MR. It has been reported that LV filling pressures were not predictable by the E/E’ ratio in subjects with MR and preserved LV function,31 because E/E’ is generally increased in such patients caused by increased flow across the regurgitant valve. Also, patients with chronic MR have preserved LV relaxation and decreased LV stiffness to compensate for the volume overload.32 These previous findings may be consistent with the findings of the present study. LA remodeling and AF are surrogate markers of LV diastolic dysfunction. Therefore, patients in the present study might have had LV diastolic dysfunction to some extent; however, gradually developing moderate-to-severe MR might cause compensatory preservation of LV relaxation as previously reported.32

Clinical Implications

Atrial functional MR has been considered to be simply caused by annulus dilatation in previous studies based on conventional 2D echocardiography.4,6,7 However, the 3D analysis of the comprehensive MV structure and dynamics in the present study allowed us to clarify more complicated characteristics of atrial MR. Epidemiological data have revealed that the worldwide prevalence and incidence of AF have been progres-
sively increasing based on global aging. In this social trend, the clinical significance of atrial functional MR may further increase in the future. Our results provided the following clinical suggestions. Considering extreme LA dilatation is the primary cause of atrial MR, therapeutic strategies to prevent or reverse the LA remodeling caused by AF should be emphasized, as previously reported. Further, PML tethering independently aggravated the atrial functional MR, along with the annulus area, and therefore, a therapeutic approach for both the annulus and leaflets, such as simultaneous annuloplasty and chordal reconstruction, may be important options for correction of atrial functional MR.

Study Limitations
Firstly, this was a retrospective, single-center study and the number of enrolled patients was relatively limited. Therefore, we could not separately analyze patients with moderate and severe atrial MR in interclass comparisons. However, we confirmed the main findings with our multivariate analysis that can continuously evaluate the effect of each variable on EROA. Also, the definition of moderate-to-severe MR has been commonly adopted in previous studies that investigated the prognosis of primary or secondary MR. Hence, we believe integrated analysis of moderate and severe MR can fit clinical practice. Secondly, patients with moderate-to-severe atrial MR had a slightly larger LVEDV than the other groups. However, these measurements were within the normal range and multivariate analysis revealed that PML tethering and MA dilatation were independent determinants of ERO even after adjusting for the LVEDV and LVEF. Therefore, these MV morphological changes are unrelated to LV remodeling and independently contribute to the development of atrial functional MR. Thirdly, the 3D data sets were acquired in a zoom mode in the patients who continued an AF rhythm during the follow-up investigation. Consequently, the 3D image analysis was in line with the methodology of a previous study that investigated the MV dynamics in atrial functional MR. Finally, there were differences in the MA measurements during the cardiac cycle between the control subjects and patients with AF; however, an AF rhythm itself might have an effect on the dynamics of the MA. Further investigation with a larger number of subjects using the latest 3D-TEE machines that are able to obtain 3D images with a higher frame rate during a single cardiac beat are desirable to confirm the results of the present study.

Conclusions
Atrial functional MR caused by LA remodeling by longstanding persistent AF consisted of multiple alterations in the static morphology and dynamics of the MV. In particular, atrigenic PML tethering was the most influential deterioration factor in atrial functional MR, along with MA dilatation.

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Disclosures
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