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Mitral Regurgitation Associated with Mitral Annulus Remodeling and Left Atrial Dilatation

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Background: Atrial functional mitral regurgitation (MR) involves functional MR with left atrial (LA) dilatation and mitral annulus (MA) remodeling. The relationship between LA dilatation and MA remodeling, and the mechanism of MR associated with MA remodeling, are unclear and were investigated in this study.
Methods: This single-center, cross-sectional retrospective study prospectively enrolled 97 consecutive patients with atrial fibrillation (AF) referred for three-dimensional transesophageal echocardiography. Mitral valve echocardiographic data of 18 AF patients with moderate or severe MR (MR group) and 79 with mild or less severe MR (non-MR group) were analyzed.
Results: The LA volume index was larger and tenting height was lower in the MR group than in the non-MR group (63.9±17.9 mL/m^2 vs. 43.6±13.9 mL/m^2; $p<0.001$; 3.9 mm vs. 4.9 mm; $p = 0.041$). Anteroposterior (AP) diameter, annulus area, and sphericity index (AP diameter/anterolateral-posteromedial diameter) of MA were larger in the MR group than in the non-MR group (30.1 mm vs. 26.4 mm; $p<0.001$; 8.8 cm^2 vs. 7.4 cm^2; $p = 0.002$; 80.1% vs. 74.5%; $p<0.001$, respectively). Linear regression analysis indicated that AP diameter was moderately correlated with LA volume index ($R = 0.535$, $p<0.001$). The area under the receiver operating characteristics curve of the AP diameter for the association with significant MR was significantly larger than that for the annulus area (0.8003 vs. 0.7180; $p = 0.003$). Multivariable analysis revealed that AP diameter ($p = 0.006$) and sphericity index ($p = 0.041$) were independently associated with significant MR, but annulus area was not ($p = 0.083$).
Conclusions: LA dilatation correlated with MA remodeling, primarily via enlargement of AP diameter. Circular change with AP diameter enlargement in MA may be a key mechanism of MR associated with MA remodeling. (J Nippon Med Sch 2025; 92: 145–153)

Key words: atrial functional mitral regurgitation, mitral annulus, atrial fibrillation

Introduction

The mechanism of mitral regurgitation (MR) can be divided broadly into two categories-organic MR and functional MR-on the basis of whether the mitral leaflets exhibit significant pathological abnormality[1]. The main mechanism of functional MR is considered disease of the subvalvular apparatus with leaflet tethering and left ventricular (LV) dysfunction[2]. However, left atrial (LA) dilatation and corresponding mitral annulus (MA) dilatation alone may cause MR in patients with long-term atrial fibrillation (AF) without LV dysfunction[3]. Such functional MR with LA dilatation without organic leaflet disease or LV dysfunction is called atrial functional MR (AFMR)[4].

Long-term loading associated with persistent AF leads to progression of LA dilatation[5], although alterations in MA morphology associated with LA dilatation have not been fully characterized. MA remodeling is usually described as a dilatation of the annulus area, and contro-

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versy exists as to whether dilatation of the annulus area alone will result in MR[2,3]. However, MA has a complex appearance: nonplanar, saddle-shape, and elliptical. In addition, the relationship between MR and MA geometry has not been carefully investigated. Therefore, we investigated the association between MA remodeling and LA dilatation, and the mechanism of MR associated with MA remodeling.

Methods

Patient Population

A single-center, cross-sectional retrospective study was performed. Patients who were scheduled to undergo catheter ablation or electrical cardioversion for AF at Nippon Medical School Hospital between June 2015 and September 2016 and underwent both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) before the procedure were eligible to participate in a study of LA dilatation without LV dilatation. Duration of persistent AF was defined as the interval from the first documented episode of persistent AF to the date of the last follow-up or initiation of treatment. For patients who were asymptomatic, onset was estimated from the first routine electrocardiogram that detected AF. Exclusion criteria were a left ventricular ejection fraction (LVEF) <50% or a history of myocardial infarction, hypertrophic cardiomyopathy, organic valve disease, prior cardiovascular surgery, or pericardial or congenital heart disease.

We analyzed data from 97 consecutive patients who were referred for three-dimensional (3D) TEE and analyzed for MA. Patients were divided into an MR group and non-MR group according to the severity of MR. Eighteen patients who had significant (moderate in 18, severe in 0) MR were analyzed as the MR group. All patients with significant MR exhibited normal mitral leaflet motion without prolapse or tethering and were classified as Carpentier type I[1]. The other 79 with mild or less severe MR were classified as the non-MR group.

This study conforms with the principles outlined in the Declaration of Helsinki and was approved by the ethics committee of the Nippon Medical School Hospital (approval number: B-2024-908). Participants were provided with explanations regarding the study, and consent was obtained using an opt-out form.

Echocardiography

Images were acquired using a Philips iE33 imaging platform with S5-1 and X7-2 transducers (Philips, Andover, MA). Two-dimensional (2D) TTE and TEE images were acquired in accordance with previously published guidelines[1,6]. LV and LA volumes were measured by the modified Simpson's rule in the apical four-chamber and two-chamber views. Quantification of the MR was performed as recommended by the American Society of Echocardiography, using an integrated method that including measurement of the vena contracta width and the area ratio of the MR jet area-to-LA area (MRJA/LAA) in mid-systole[1]. Significant MR was defined as either moderate or severe MR. Moderate MR was characterized by an MRJA/LAA ratio >20% and a vena contracta width >3 mm. Severe MR was defined as an MRJA/LAA ratio >50% and a vena contracta width >7 mm, in accordance with the guideline[7]. TEE was performed with the patient under conscious sedation, ensuring that systolic blood pressure was maintained throughout the examination.

Quantitative Analysis of the MA Based on 3D TEE

Because of the presence of AF, we used the one-beat real-time 3D zoomed mode to avoid stitch artifacts. Datasets were analyzed according to current guidelines[8]. Care was taken to obtain the highest possible frame rate while including the entire MV. The 3D datasets were stored digitally in raw data format for offline analysis with commercially available software (QLab, Mitral Valve Quantification; Philips). Using frame-by-frame motion, we analyzed 3D datasets of the MV in end-systole (the frame immediately prior to MV opening)[9,10]. The MV dataset was displayed in multiplanar review mode. After adding anatomical landmarks for the MA and aorta, the software created 16 static points of the MA and a model of the MA ring. Each point of the MA was manually adjusted on the motion picture because they were identified as hinge points of the mitral leaflets[11,12]. Finally, the parameters of MA geometry were automatically measured. Quantitative parameters of MA geometry were anteroposterior (AP) diameter (A2-to-P2 distance, minor diameter); anterolateral-posteromedial (ALPM) diameter (intercommissural distance, major diameter); sphericity index (calculated by dividing the AP by the ALPM diameters); circumference; annulus area (assessed by projecting the contour onto a plane); annular height (the vertical distance between the lowest and highest points of the annulus); and saddle-shape ratio (calculated by dividing the annular height by the ALPM diameter) (**Fig. 1**)[13–15].

Statistical Analysis

Data were analyzed using JMP Pro v11.2 (SAS Institute Inc., Cary, NC, USA) and expressed as mean±SD when normally distributed. Differences between both groups

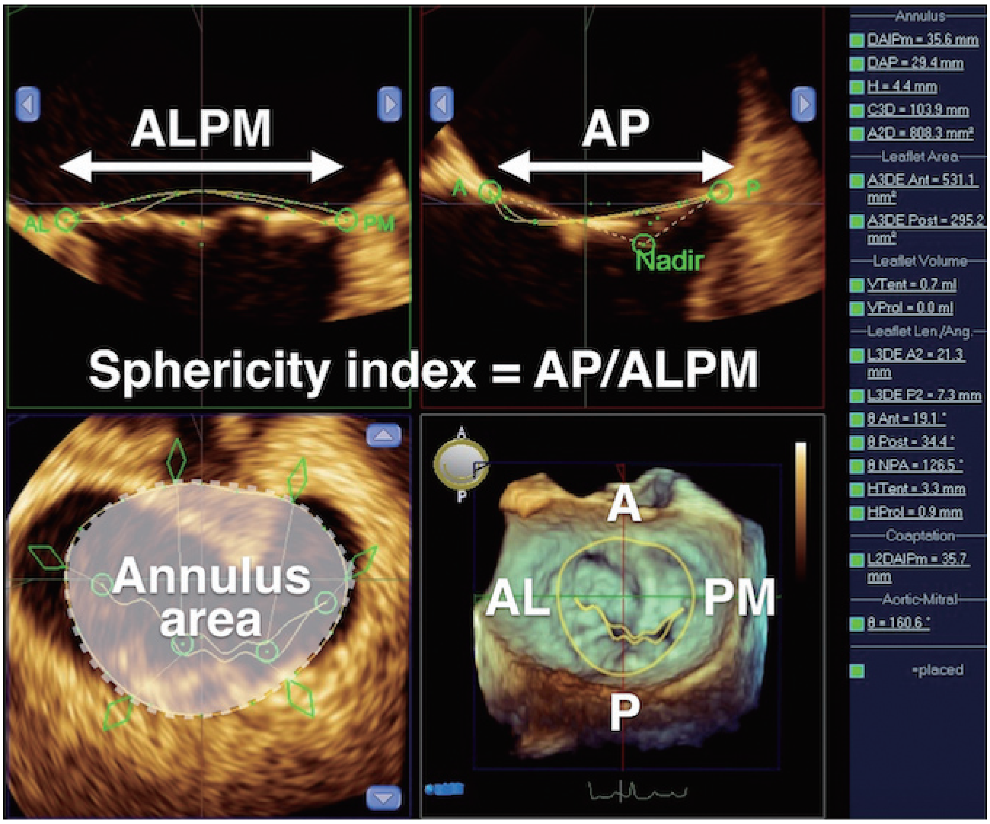

Fig. 1 Quantitative 3D analysis of the MA: multiplanar review mode. Quantitative parameters of MA geometry were AP diameter; ALPM diameter; sphericity index (calculated by dividing the AP by the ALPM diameters); circumference; annulus area (assessed by projecting the contour onto a plane); annular height; and saddle-shape ratio (calculated by dividing the annular height by the ALPM diameter).
MA, mitral annulus; AP, anteroposterior; ALPM, anterolateral-posteromedial.

were analyzed using the Student t test or Pearson chi square test. Correlations between parameters of MA geometry and left atrial volume index (LAVI) were assessed with simple linear regression analysis. To explore the association of each MA parameter with significant MR for patients with AF, unadjusted and adjusted logistic regression analyses were performed. Variable selection for univariate and multivariable analyses was based on significant differences in MA geometry parameters in initial comparisons between the MR and non-MR groups. An adjusted regression model was constructed by using the risk factors for significant MR (age, LAVI, and tenting height), based on clinical relevance and significant differences in initial comparisons of patient characteristics. Tenting height has a general correlation with the severity of functional MR[1]. Receiver operating characteristics (ROC) curve analysis was performed to evaluate the relationship between significant MR and MA parameters, and the areas under the curves (AUCs) were compared. ROC curve analysis was conducted using standard methods, and AUCs were compared with the DeLong test for two correlated ROC curves. Variables that were significant in the adjusted logistic regression were selected and compared with the commonly used MA area[2] as a marker for annular enlargement.

Results

Patient and Echocardiographic Characteristics

The characteristics of the patients are shown in **Table 1**. Mean age was 67.8±8.4 years. Persistent AF was present in 46 patients, and mean duration of persistent AF was 2.5±4.3 years. The duration of persistent AF was longer in the MR group than in the non-MR group. LAVI was larger in the MR group than in the non-MR group (63.9±19.7 mL/m^2 vs. 43.6±13.9 mL/m^2; $p < 0.001$). Although LV end-diastolic volume was larger in the MR group than in the non-MR group, there was no significant difference in LV end-systolic volume or LVEF between groups. Tenting height was lower in the MR group than in the non-MR group (3.9±1.8 mm vs. 4.9±1.8 mm, $p = 0.041$).

Table 1 Patient Characteristics

	All (n = 97)	MR group (n = 18)	Non-MR group (n = 79)	p-value (MR vs. non-MR)
Clinical characteristics				
Age, years	67.8 ± 8.4	70.4 ± 5.2	67.2 ± 8.9	0.149
Male, n (%)	67 (69%)	11 (61%)	56 (71%)	0.418
Body surface area, m^2	1.73 ± 0.19	1.71 ± 0.23	1.73 ± 0.18	0.620
Persistent AF	46 (47%)	10 (56%)	36 (46%)	0.444
Duration of persistent AF, y	2.5 ± 4.3	5.2 ± 7.6	1.7 ± 2.2	0.023
Echocardiography				
LA diameter, mm	39.8 ± 6.6	43.6 ± 7.0	38.9 ± 6.2	0.007
LA volume index, mL/m^2	47.4 ± 16.4	63.9 ± 19.7	43.6 ± 13.9	<0.001
LV end-diastolic diameter, mm	46.7 ± 5.8	48.3 ± 8.0	46.3 ± 5.2	0.179
LV end-systolic diameter, mm	28.8 ± 4.8	29.4 ± 6.3	28.6 ± 4.5	0.523
LV end-diastolic volume index, mL/m^2	39.7 ± 13.5	47.1 ± 17.1	38.1 ± 12.2	0.018
LV end-systolic volume index, mL/m^2	14.9 ± 6.1	16.9 ± 6.7	14.5 ± 5.9	0.157
LV ejection fraction, %	62.7 ± 6.5%	64.9 ± 6.9%	62.2 ± 6.3%	0.110
MRJA/LAA, %	10.3 ± 10.4%	26.0 ± 3.3%	6.7 ± 7.9%	<0.001
Vena contracta width, mm	1.6 ± 1.7	4.2 ± 1.4	1.1 ± 1.2	<0.001
Tenting height, mm	4.7 ± 1.8	3.9 ± 1.8	4.9 ± 1.8	0.041
Mitral annulus parameters				
AP diameter, mm	27.0 ± 3.4	30.1 ± 3.5	26.4 ± 3.0	<0.001
ALPM diameter, mm	35.8 ± 3.9	37.3 ± 4.4	35.4 ± 3.7	0.057
Circumference, cm	10.2 ± 1.1	10.8 ± 1.2	10.1 ± 1.0	0.007
Annulus area, cm^2	7.8 ± 1.7	8.8 ± 2.0	7.4 ± 1.5	0.002
Sphericity index, %	75.8 ± 6.7	80.1 ± 5.1	74.5 ± 6.6	<0.001
Annulus height, mm	4.5 ± 1.3	4.4 ± 1.3	4.5 ± 1.3	0.623
Saddle-shape ratio, %	12.7 ± 3.8	11.8 ± 3.6	12.9 ± 3.9	0.254

Values are mean ± SD or n (%).
MR: mitral regurgitation, AF: atrial fibrillation, LA: left atrium, LV: left ventricle, MRJA: mitral regurgitation jet area, LAA: left atrium area, AP: anteroposterior, ALPM: anterolateral-posteromedial

Quantitative Parameters of MA Based on 3D TEE

AP diameter was longer in the MR group than in the non-MR group (30.1±3.5 mm vs. 26.4±3.0 mm, p <0.001) (**Table 1**). ALPM diameter tended to be longer in the MR group, but the difference was not significant. Therefore, the sphericity index was greater in the MR group than in the non-MR group (80.1±5.1% vs. 74.5±6.6%, p <0.001). The circumference and annulus area were larger in the MR group than in the non-MR group (10.8±1.2 cm vs. 10.1±1.0 cm, p = 0.007; and 8.8±2.0 cm^2 vs. 7.4±1.5 cm^2, p = 0.002, respectively). There were no significant differences in annular height or saddle-shape ratio between groups. **Figure 2** shows the typical MA morphology in 2D and 3D images of patients with and without significant MR.

Association between LA Size and MA Morphology

The correlations of LAVI with MA parameters are shown in **Figure 3**. A simple linear regression indicated that AP diameter, ALPM diameter, circumference, annulus area, and sphericity index were significantly positively correlated with LAVI. AP diameter was moderately correlated with LAVI (R = 0.535; p <0.001). However, ALPM diameter was weakly correlated with LAVI (R = 0.309).

Parameters of MA Geometry Associated with MR

Table 2 shows the results of the unadjusted and adjusted regression analyses. AP diameter (odds ratio [OR], 1.46 per mm; 95% CI, 1.11-2.04 per mm; p = 0.006) and sphericity index (OR, 1.11 per %; 95% CI, 1.01-1.25 per %; p = 0.041) were independently associated with significant MR; however, circumference (OR, 1.78 per cm; 95% CI, 0.87-3.94 per cm; p = 0.119) and annulus area were not (OR, 1.49 per cm^2; 95% CI, 0.95-2.46 per cm^2; p = 0.083).

In receiver operator characteristics curve analysis of the relationship between significant MR and MA parameters (**Fig. 4**) the AUC was highest for AP diameter (0.8003; 95% CI, 0.6450-0.8984), followed by the AUC of the sphericity index (0.7609; 95% CI, 0.6274-0.8574). The AUC for annulus area, which was the most common parameter of MA dilatation, was significantly lower than

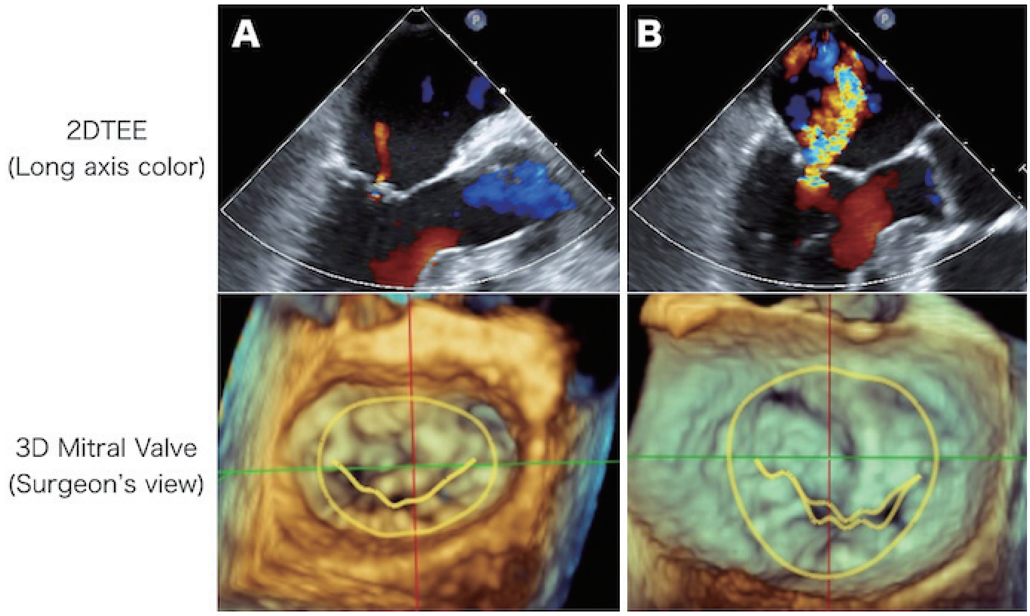

Fig. 2 Differences in MA morphology in relation to the presence of significant mitral regurgitation. The 2D long-axis color view (top) and 3D image (bottom) of the MV on 2D TEE are shown. (A) Example of trivial MR. (B) Example of moderate MR. This patient had an MA with large dimensions and greater sphericity.
MA, mitral annulus; MV, mitral valve; MR, mitral regurgitation; 2D TEE, 2-dimensional transesophageal echocardiography.

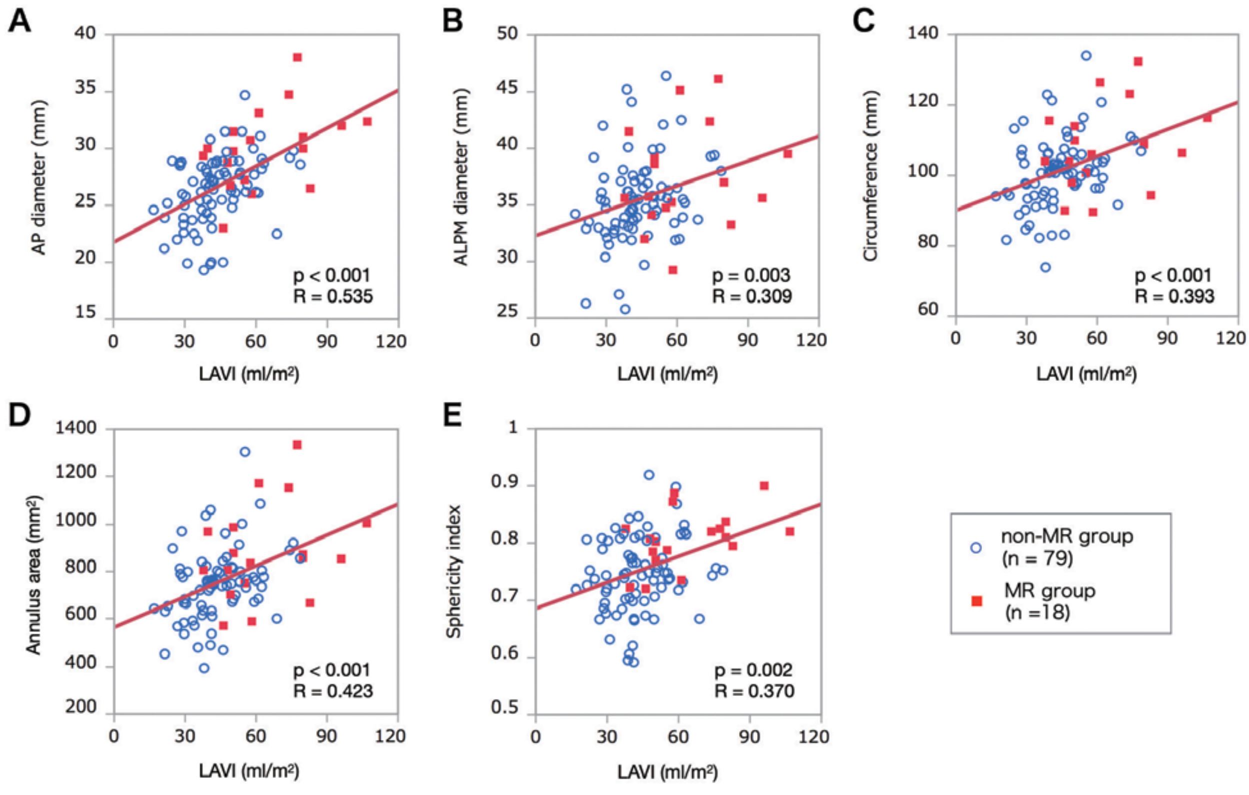

Fig. 3 Correlations of LA volume index with MA parameters. All MA parameters showed a significantly positive correlation with the LA volume index. AP diameter was the parameter most moderately correlated with LA volume index, more so than annulus area.
LA, left atrium; MA, mitral annulus; AP, anteroposterior; MR, mitral regurgitation.

Table 2 Univariable and multivariable regression models of the predictive capacity of MA parameters for significant MR

	Univariable			Adjusted for age, LAVI, and tenting height		
	OR	95% CI	p-value	OR	95% CI	p-value
AP diameter (+1 mm)	1.51	1.23-1.96	<0.001	1.46	1.11-2.04	0.006
Circumference (+1 cm)	1.95	1.19-3.37	0.008	1.78	0.87-3.94	0.119
Annulus area (+1 cm^2)	1.59	1.17-2.26	0.003	1.49	0.95-2.46	0.083
Sphericity index (+1%)	1.17	1.07-1.31	<0.001	1.11	1.01-1.25	0.041

MA: mitral annulus, MR: mitral regurgitation, MRJA: mitral regurgitation jet area, LAA: left atrial area, AF: atrial fibrillation, LAVI: left atrial volume index, AP: anteroposterior, OR: odds ratio, CI: confidence interval

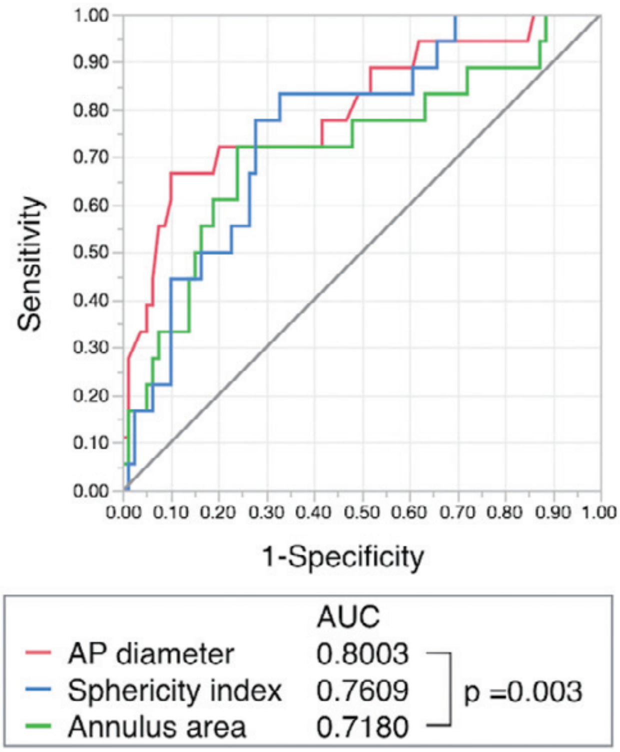

Fig. 4 ROC curves of AP diameter and sphericity index and annulus area for the association with significant MR in patients with AF. ROC curve analysis showed that the AUC of AP diameter was significantly greater than that of the annulus area.
ROC, Receiver-operating characteristics; AP, anteroposterior; MR, mitral regurgitation; AF, atrial fibrillation; AUC, area under the curve.

that for AP diameter (0.7180, p = 0.003).

Discussion

This study provides a detailed description of MA geometry based on 3D TEE for a large number of patients with AF and found an association between MA remodeling and LA dilatation and the mechanism of MR associated with MA remodeling for patients with AF. The main results of the study are that (1) patients with significant MR had larger LA, larger MA geometry, and lower tenting height than patients without MR; (2) for patients with AF, LA dilatation was correlated with MA remodeling, primarily via enlargement of AP diameter; and (3) AP diameter and sphericity index were independently associated with significant MR, but annulus area was not.

AF is one of the most common disorders of cardiac rhythm and causes expansion of the LA[4,5,16]. Previous studies have shown that LA dilatation results in MA enlargement[2,3,9,17,18]. The MA is enclosed on both sides by the left and right fibrous trigones, and the anterior side of the MA is anatomically connected with the aortic annulus via the aortomitral curtain[19]. Consequently, the posterior side of the MA is relatively weak because it lacks a fibrous cord, potentially rendering the posterior side of the MA susceptible to enlargement[20]. In this study, LA dilatation correlated with MA remodeling, primarily via enlargement of AP diameter. Furthermore, the shape of the MA was more circular because of the greater enlargement of AP diameter relative to ALPM diameter. Although the association between annulus area and MR was not significant in the present study, its inclusion is crucial in providing a comprehensive evaluation of mitral annular geometry in relation to historical perspectives of functional MR[2].

The MA is important in leaflet coaptation and enlargement, which leads to incomplete MV closure in MR[19]. A recent study of non-ischemic functional MR noted that functional MR could be produced in a porcine beating heart model with multiple small incisions in the MA, resulting in dilatation and 3D changes in MA geometry, primarily in relation to AP diameter[21]. Using receiver operator characteristic curve analysis for MR, AP diameter, and sphericity index, we found a stronger association with significant MR than with annulus area (**Fig. 4**). All MRs observed in this study were AFMR because patients with LA dilatation had no organic leaflet disease or LV dysfunction. Similarly, Mihaila et al.[10] reported that patients with organic MR presented with a larger and more spherical MA than did control patients, and that MA remodeling is directly associated with MR severity in patients with organic MR. Such findings suggest that MA remodeling and MR are interrelated.

Tenting height is an important marker of functional MR because leaflet tethering is thought to be the primary mechanism responsible for functional MR with LV dysfunction (ventricular functional MR). However, in this study, tenting height was much lower in the MR group than in the non-MR group. Although the mitral leaflets could unfold to maintain coaptation and compensate for the increased annular size by reducing tenting height until a certain level, at which point the leaflets could no longer overcome the increased annular dimensions and MR would leak out[9].

To explore independent associations between each parameter of MA and MR for patients with AF, we used an adjusted logistic regression model that used tenting height as the risk factor for functional MR. AP diameter and sphericity index were independently associated with MR, while annulus area was not. These results suggest that circular change with AP diameter enlargement in MA is a key mechanism of MR associated with MA remodeling.

The definition of MA dilatation remains unclear because of the limited data on the normal range of MA dimensions[22,23]. However, 3D analyses of the MA performed in this study and previous studies are complicated, time-consuming, and difficult to conduct in daily practice. Recently, Foster et al.[24] reported that AP diameters from 3D computed tomographic analysis were strongly correlated with those derived from anatomically appropriate measurements using 2D TTE. Therefore, AP diameter measured using 2D TTE may be a straightforward and useful indicator of MA enlargement.

As described in a recent review[25], AFMR is generally thought to lack mitral valve tethering and instead exhibit flattening, which is consistent with the present findings, which suggest that while changes in MA sphericity contribute to atrial functional MR, other mechanisms, such as atriogenic posterior leaflet tethering, may also be significant, as noted in previous studies[26–28]. The present data, however, showed no significant mitral valve tethering in cases of MR. Given that the patients in this cohort were scheduled for catheter ablation or electrical cardioversion, they were younger and had smaller left atrial sizes than those in other studies[9,26,29]. Consequently, the severity of MR in our cohort remained moderate. Thus, morphological changes in MA identified in this study may represent early or initial alterations in AFMR. It is possible that more severe forms of AFMR develop through additional mechanisms, such as posterior leaflet tethering, that were not detectable in the current cohort because of its specific characteristics.

An additional mechanism is insufficient leaflet remodeling in response to annular dilatation. Kagiyama et al.[29] reported that insufficient leaflet remodeling in response to annular dilatation was strongly associated with MR severity. 3D analysis of the comprehensive MV structure and dynamics will improve understanding of the complex characteristics of AFMR.

A clearer understanding of MA geometry is becoming increasingly important for successful surgical and percutaneous treatment of MR. Improved understanding of alterations in annular geometry and dynamics, which occur in functional and ischemic MR, has had a considerable impact on annuloplasty ring design[19]. Recently, percutaneous treatment was shown to reduce MR severity and improve functional outcomes[30], and percutaneous treatment with the MitraClip device has been reported to be effective for patients with AFMR[31]. Additionally, the reduction in MA size achieved by the MitraClip in functional MR patients was associated with decreased MR severity[32]. Consequently, analysis of MA geometry may help further improve treatment strategies.

Limitations

This single-center, cross-sectional study analyzed data from a limited number of patients. Quantification of MR severity for patients with AF and MR is problematic because of the variability in stroke volume, as regurgitation originates along the line of apposition and is not focused in one region[9]. Although the MR jet area has been frequently used in similar studies of AF and MR, it is susceptible to variability introduced by LA size and compliance, blood pressure, volume status, and the color Doppler scale set by the ultrasonographer. The threshold for defining severe MR in these patients needs further study. The 3D datasets were acquired in zoom mode for patients with a persistent AF rhythm during echocardiography. Given the limitations of multi-beat acquisition in patients with AF, frame rates in single-beat qualitative images, as used here, may affect the reproducibility of the present results. However, the 3D image analysis was consistent with the methodology of a previous study of MV dynamics in MR in patients with AF[9,25].

Conclusions

LA dilatation correlated with MA remodeling, primarily because of the increase in AP diameter. Circular change with AP diameter enlargement in MA may be an essential mechanism of MR associated with MA remodeling.

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Conflict of Interest: None.

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