Insufficient Leaflet Remodeling in Patients With Atrial Fibrillation

Association With the Severity of Mitral Regurgitation

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Background**—**The relationship between annular dilatation caused by atrial fibrillation (AF) and mitral regurgitation (MR) remains controversial. We hypothesized that the small ratio of total leaflet area/annulus area (TLA/AA), reflecting insufficient leaflet remodeling to annular dilatation, is a main component of MR in patients with AF.

Methods and Results**—**Three-dimensional transesophageal echocardiographic data of the mitral valve were analyzed in 28 AF patients with moderate or severe MR (MR group), age- and sex-matched 56 AF patients with mild or less MR (non-MR group), and 16 control subjects. AA was significantly greater in both the MR (645±126 mm^2/m^2, P<0.001) and non-MR groups (568±121 mm^2/m^2, P=0.001) compared with control subjects (444±108 mm^2/m^2). However, TLA/AA was significantly smaller in the MR (1.29±0.10, P<0.001), but not in the non-MR group (1.65±0.24, P>0.99), compared with control subjects (1.70±0.29). In linear regression analysis, TLA/AA was inversely associated with the effective regurgitant orifice (r=−0.73, P<0.001). The area under the receiver-operating-characteristics curve of TLA/AA was significantly greater than that of AA (0.95 versus 0.72, P<0.001). Multivariable analysis revealed that small TLA/AA (P<0.001) was independently associated with significant MR, while AA was not (P=0.26).

Conclusions**—**In patients with AF, insufficient leaflet remodeling to annular dilatation, rather than crude annular dilatation, was strongly associated with the severity of MR. **(*Circ Cardiovasc Imaging*. 2017;10:e005451. DOI: 10.1161/CIRCIMAGING.116.005451.)**

Key Words: 3-dimensional echocardiography ■ atrial fibrillation ■ dilatation ■ echocardiography ■ mitral valve regurgitation

Atrial fibrillation (AF) is a common cardiac rhythm disorder, found prominently among elderly patients and patients with heart failure. Prevalence of AF is increasing as society is aging and is predicted to double for the next 20 years.[1] Research shows that AF causes left atrial (LA) and mitral annular dilatation[2]; however, the relationship between annular dilatation caused by AF and mitral regurgitation (MR) still remains controversial.

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Typically, isolated annular dilatation due to AF had been recognized as a benign morphological change, which does not usually cause significant MR. Otsuji et al[3] studied 25 patients with lone AF and reported that, despite the fact that they had a significantly enlarged mitral annulus similar to patients with functional MR due to ischemic cardiomyopathy, none of the patients with AF had significant MR. In light of these findings, they concluded that annular dilatation due to AF does not typically cause significant MR.

However, recent articles have continuously reported that functional MR in patients with AF without left ventricular (LV) dysfunction certainly exists and, in some cases, becomes severe.[4–6] These articles were focusing on AF patients with significant MR and reported that their mitral annuluses were significantly dilated.

Considering these two seemingly dissimilar theses, we hypothesized that, while annular dilatation is a requisite condition for the occurrence of MR in patients with AF, there are typically other contributing factors to this condition as well.

Functional MR due to LV dysfunction or dilatation is one of the most common valvular heart diseases in developed countries, and even moderate functional MR is reported to be associated with a poor prognosis.[7] In functional MR, mitral leaflet remodeling, or leaflet elongation, has been reported as a compensating mechanism for the dilated LV and annulus, as insufficient leaflet remodeling has been reported to be associated with the severity of functional MR.[8,9]

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Methods

Study Population

We reviewed patients who underwent clinically indicated transesophageal echocardiography (TEE) in our hospital between April 2014 and September 2015. There were 268 patients with the following 4 characteristics: (1) medical history of AF that was detected by ECG at least once, (2) normal LV size and contraction (LV ejection fraction >50% and LV end-diastolic diameter <55 mm) without regional wall motion abnormalities, (3) absence of congenital anomaly or degenerative change (prolapse, rheumatic change, or severe calcification) of mitral valve by 2-dimensional (2D) echocardiography, and (4) absence of severe other valvular disorders. The definition of prolapse, rheumatic change, and severe calcification were as follows: (1) prolapse–leaflets deviated 2 mm above the annular plane in a long-axis view[10]; (2) rheumatic change–at least two of (a) restricted leaflet mobility, (b) focal or generalized valvular thickening, and (c) abnormal subvalvular thickening[11]; and (3) severe calcification–calcification on the valve >5 mm in any direction.[12] Persistent AF was defined as continuous AF that is sustained >7 days.[5,13] Among them, 40 patients had moderate or severe MR. Severity of MR was assessed using the effective regurgitant orifice and vena contracta width, as mentioned below. After exclusion of the five patients with systolic anterior motion of the mitral valve and seven patients with insufficient 3D data set, 28 patients were included in the analysis as the MR group. From the other 228 patients who met the previous four criteria and had mild or less MR, we sampled age-matched (±2 years) and sex-matched 56 patients as the non-MR group (1 MR and 2 non-MR groups). We also studied 16 patients with sinus rhythm who underwent TEE to assess for a cardiac source of embolic events and were diagnosed with a normal mitral valve (control group).

We obtained approval from the Investigational Review Board Committee of the Sakakibara Heart Institute of Okayama for the collection and publication of data.

Image Acquisition and Analysis

Transthoracic 2D echocardiographic images were acquired in accordance with published guidelines.[14,15] In all the study subjects, we acquired 3D TEE images under mild sedation using an iE33 ultrasound system and X7-2t transducer (Philips Medical Systems, Andover, MA). The probe was positioned at the midesophageal level, taking care to include the entire mitral valve, while the mid- and apical LV segments were excluded to maximize the volume rate. We used multibeat (2–6 beats) acquisition because of its high volume rate. For patients with AF rhythm and patients who could not stop breathing during the examination, we used one beat real-time 3D zoomed mode to avoid stitch artifacts.

Acquired datasets were analyzed off-line using commercially available semiautomated software, MVN (Philips Medical Systems), by experienced observers blinded to clinical data. We previously reported that reproducibility of mitral valve analysis was high while using this software. The interobserver agreements of annular and leaflet parameters assessed using Cronbach's α were high (0.82–0.97).[16] Leaflet area and length were measured in end-diastole (one frame before the leaflets were coapted) because in systole, the whole leaflet area cannot be visualized[9] (Figure 1A). Annulus and prolapse/tenting parameters were measured in midsystole (Figure 1B). To test whether leaflet area increased relative to changes in the mitral annulus, we calculated the ratio of total leaflet area/annular area (TLA/AA) as previously described[8,17]; small TLA/AA indicates insufficient leaflet remodeling compared with annular dilatation. In the patients who were in AF rhythm during examination, we used the beat in heart rate ≈70 to 80 bpm.

Thicknesses of the anterior and posterior mitral valve were measured at both clear and rough zones in end-diastole using multiplanar reconstruction images from the 3D data set (Figure 1C). These 3D parameters were compared after being divided by body surface area.

The MR grade was then evaluated by comprehensive approach using effective regurgitant orifice calculated by proximal isovelocity surface area method or vena contracta width as recommended in the guidelines.[14,15,18] For the vena contracta width measurements, we used the long-axis view that is perpendicular to the commissural line.[14,15] An

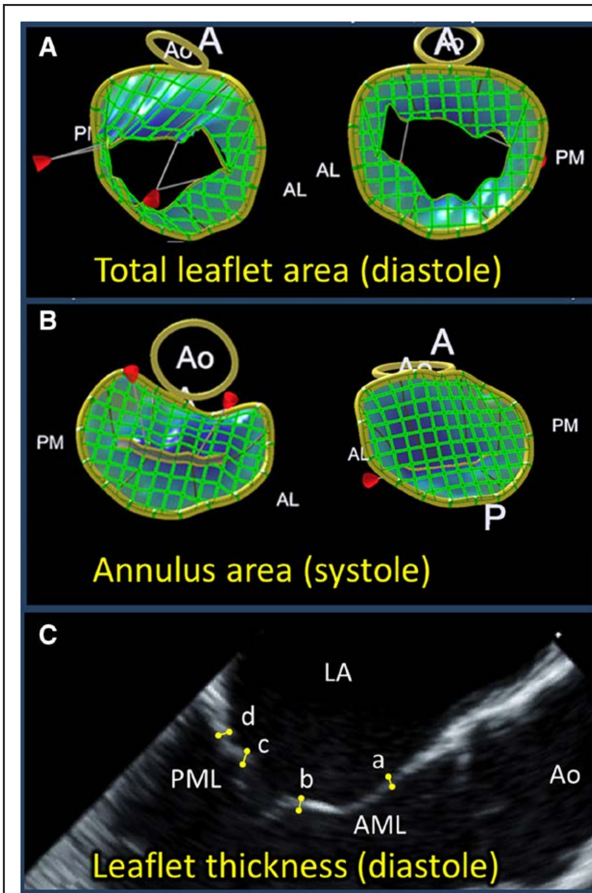

Figure 1. Three-dimensional (3D) analysis of mitral valve. **A**, Leaflet parameters were measured in end-diastole, because in systole, the area of each leaflet involved in coaptation cannot be visualized uniformly. **B**, Parameters of annulus were measured in midsystole. **C**, Thickness of the anterior and posterior mitral valve was measured at both clear (a and d) and rough zone (b and c) in end-diastole using multiplanar reconstruction images from 3D data set. A indicates anterior; AL, antero-lateral; AML, anterior mitral leaflet; Ao, ascending aorta; LA, left atrium; P, posterior; PM, postero-medial; and PML, posterior mitral leaflet.

effective regurgitant orifice as ≥0.2 cm^2 and a vena contracta width ≥ 3 mm were considered diagnostic of significant (moderate or severe) MR.

The echocardiographic equipment was managed according to the guidelines of the Japanese Society of Echocardiography.[19]

Statistical Analysis

Data are presented as means±SD for continuous variables and as frequency (%) for categorical variables. One-way ANOVA and Student *t* test with post hoc Bonferroni correction was used to compare continuous variables with a normal distribution among the 3 groups and between 2 groups, respectively. Mann–Whitney *U* test was used to compare the duration of AF. The χ^2 test or Fisher exact test was used to compare categorical variables. Correlation between TLA/AA and effective orifice area was assessed with Pearson's correlation test and univariable linear regression analysis in patients with AF and effective regurgitant orifice >0 cm^2. The receiver-operating characteristics curve for each parameter was constructed to examine whether TLA/AA predicted the occurrence of MR in patients with AF better than the crude AA or TLA, and the areas under the curves were compared according to the method of DeLong et al.[20] An appropriate cut-off value to predict the occurrence of MR in patients with AF was then decided according to the Youden index. To explore the independent association between TLA/AA and significant MR in patients with

AF, a multivariable logistic regression model was constructed by using the previously reported risk factors for MR in patients with AF (annular area, persistent versus paroxysmal AF, and LA volume index).[6,21] Although age was also reported as a risk factor, we exclude age from the model because age was used to match the MR and non-MR groups. The stability of this multivariable model was assessed using a variance inflation factor. To investigate the mechanisms of MR in patients with AF, receiver-operating characteristics analysis and logistic regression analysis were assessed in only AF patients, whereas control subjects were excluded from these analyses. All statistical analyses were performed with R (The R Foundation for Statistical Computing, Vienna, Austria) and its graphical user interface, EZR (version1.27; Saitama Medical Center, Jichi Medical University, Saitama, Japan).[22] In all analyses, $P<0.05$ was taken to indicate statistical significance.

Results

Patient Characteristics

Table 1 presents the various characteristics found among patients. Age, sex, and body surface area were similar among the 3 groups. There were significant differences in the prevalence of hypertension, LV and LA size. Compared with the non-MR group, the MR group had greater LA diameter (45.7±7.7 versus 39.7±6.2 mm, $P<0.001$) and LA volume index (50.5±19.5 versus 34.0±15.7 mL/m^2, $P<0.001$). There was no significant difference in the prevalence of persistent AF and the duration of AF (median [quartile range], 11 [1–23] versus 10 [4.75–25.5], $P=0.47$) between the MR and non-MR groups.

TEE Parameters

Mean volume rate of TEE images was 19.7±9.2 (10–34) vps. At the time of TEE, blood pressure was similar among the 3 groups (Table 2) and the rate of the patients in AF rhythm was not significantly different between the MR and non-MR groups (16/28 versus 26/56, $P=0.49$). Table 2 shows mitral valve parameters assessed by TEE, highlighting that all annulus parameters, except for the annulus height, were greatest in the MR group and smallest in the control group.

AA was significantly greater in both the MR (645±128 mm^2/m^2, $P<0.001$) and non-MR groups (568±121 mm^2/m^2, $P=0.001$) compared with the control group (444±108 mm^2/m^2). However, there were significant overlaps among the 3 groups, making it difficult to distinguish the groups solely based on AA (Figure 2A). TLA was slightly, but not significantly, increased in the MR group (828±161 mm^2/m^2, $P=0.06$) compared with the control group (741±169 mm^2/m^2), whereas it was significantly increased in the non-MR group (929±202 mm^2/m^2, $P=0.002$; Figure 2B). TLA in the entire patients with AF was significantly larger than the control group (895±195 versus 741±169 mm^2/m^2, $P=0.004$). If leaflet remodeling does not occur in patients with AF, the leaflet area could not be different among the groups. These findings suggested that leaflet remodeling occurs in patients with AF.

The correlation between the TLA and the AA was strong ($r=0.74$ in the whole cohort and 0.92 in the MR group). This

Table 1. Patient Characteristics

	MR Group (n=28)	Non-MR Group (n=56)	*P* Value*	Control (n=16)	*P* Value†
Age, y	75.9±6.4	74.9±8.0	>0.99	70.8±10.3	0.12
Male sex, n (%)	18 (64.3)	36 (64.3)	>0.99	10 (62.5)	0.99
Body surface area, m^2	1.56±0.19	1.59±0.18	>0.99	1.58±0.18	0.79
Medical history					
Hypertension, n (%)	19 (70.4)	26 (46.4)	0.21	12 (75.0)	0.049
Diabetes mellitus, n (%)	8 (29.6)	11 (19.6)	>0.99	5 (31.2)	0.51
COPD, n (%)	0 (0.0)	4 (7.1)	0.89	1 (6.2)	0.36
Persistent AF, n (%)	14 (51.9)	21 (37.5)	0.82	NA	0.19
Echocardiography					
LVDd, mm	48.8±5.7§	46.7±4.3	0.20	43.5±6.4	0.004
LVDs, mm	32.6±5.2§	30.4±3.8	0.12	28.6±4.4	0.013
LVEF, %	62.5±6.6	63.5±6.1	>0.99	63.6±5.7	0.83
LA diameter, mm	45.7±7.7‡§	39.7±6.2	<0.001	35.2±6.4	<0.001
LA volume index, mL/m^2	50.5±19.5‡§	34.0±15.7	<0.001	23.7±11.0	<0.001
AR, n (%)	2 (7.4)	2 (3.6)	0.98	0 (0.0)	0.22
AS, n (%)	2 (7.4)	2 (3.6)	>0.99	3 (23.1)	0.093
MR, n (%)	28 (100.0)‡§	0 (0.0)	<0.001	0 (0.0)	<0.001
TR, n (%)	5 (17.9)	8 (14.3)	>0.99	0 (0.0)	0.24

AF indicates atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; COPD, chronic obstructive pulmonary disease; LA, left atrium; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; and TR, tricuspid regurgitation.

**P* value between MR and Non-MR group (post-hoc analysis with Bonferroni correction).

†*P* value among 3 groups (ANOVA test).

‡ and §$P<0.05$ vs non-MR and vs control by post hoc Bonferroni correction, respectively.

Table 2. TEE Parameters

	MR Group (n=28)	Non-MR Group (n=56)	*P* Value*	Control (n=16)	*P* Value†
Vital signs at the time of TEE					
Systolic BP, mm Hg	126±20	124±14	>0.99	119±15	0.40
Diastolic BP, mm Hg	69±10	71±11	>0.99	68±10	0.35
Heart rate, bpm	75±17	69±12	0.20	70±11	0.18
AF, rhythm	16 (57.1)	26 (46.4)	>0.99	NA	0.49
Annulus parameters					
IC diameter, mm/m²	24.3±2.9§	22.8±3.3§	0.20	20.5±2.7	<0.001
AP diameter, mm/m²	20.8±3.0‡§	18.6±3.2§	0.010	16.3±2.8	<0.001
Annulus area, mm²/m²	645±126‡§	568±121§	0.023	444±108	<0.001
Circumferential length, mm/m²	75.5±9.3§	70.5±11.0	0.12	63.6±8.6	0.002
Annulus height, mm/m²	3.4±1.1	3.6±1.0	0.81	4.0±0.9	0.13
Leaflet parameters (diastole)					
Total leaflet area, mm²/m²	828±161	929±202§	0.060	741±169	0.001
AML length, mm/m²	15.7±2.6	15.6±4.0§	>0.99	12.7±4.1	0.015
PML length, mm/m²	7.9±2.0‡	9.9±2.4§	<0.001	7.4±2.6	<0.001
AML area, mm²/m²	478±81	526±139§	0.27	431±115	0.017
PML area, mm²/m²	350±100‡	404±85§	0.029	309±80	<0.001
Leaflet thickness (diastole)					
AML clear zone, mm	1.5±0.4	1.5±0.3	>0.99	1.5±0.3	0.77
AML rough zone, mm	2.6±0.6	2.4±0.5	0.21	2.3±0.7	0.14
PML clear zone, mm	1.7±0.4	1.7±0.4	>0.99	1.7±0.4	0.98
PML rough zone, mm	1.7±0.4	1.7±0.4	>0.99	1.5±0.3	0.22
Leaflet parameters (systole)					
Tenting height, mm/m²	2.48±1.11	3.08±1.19	0.060	2.85±0.66	0.07
Tenting volume, mL/m²	0.58±0.51	0.79±0.46	0.16	0.59±0.34	0.09
MR severity					
ERO, cm²	0.26±0.05‡	0.05±0.06	<0.001	NA	<0.001
VCW, mm	5.1±1.0‡	1.3±1.1	<0.001	NA	<0.001
TLA/AA	1.29±0.10‡§	1.65±0.24	<0.001	1.70±0.29	<0.001

AML indicates anterior mitral leaflet; AP, antero-posterior; BP, blood pressure; ERO, effective regurgitant orifice; IC, intercommissure; MR, mitral regurgitation; PML posterior mitral leaflet; TEE, transesophageal echocardiography; TLA/AA, the ratio of total leaflet area/annulus area; and VCW, vena contracta width.

**P* value between MR and Non-MR group (post-hoc analysis with Bonferroni correction).

†*P* value among 3 groups (ANOVA test).

‡ and §*P*<0.05 vs non-MR and vs control by post hoc Bonferroni correction, respectively.

result was concordant with the previous report (r^2=0.85 in the patients with functional MR).[9]

TLA/AA was significantly smaller in the MR group (1.29±0.10, *P*<0.001), yet consistent in the non-MR group (1.65±0.24, *P*>0.99) compared with the control group (1.70±0.29). The dot chart shown in Figure 2C reveals that this parameter had much less overlap among the groups than crude value of AA or TLA.

The tenting parameters were not significantly different and even slightly lower in the MR group, indicating that the cause of MR in patients with AF was not tethering of mitral valve. Thickness of the leaflets also remained consistent among groups.

Association Between Insufficient Leaflet Remodeling and MR in Patients With AF

In linear regression analysis, TLA/AA was significantly and inversely associated with effective regurgitant orifice (Figure 3; *r*=−0.73, *P*<0.001).

Receiver-operating characteristics curve analysis showed that the area under the curve of TLA/AA was 0.95 (95% confidence interval [CI], 0.90–0.99) and significantly higher than that of AA (0.72; 95% CI, 0.60–0.84; *P*<0.001) or TLA (0.62; 95% CI, 0.49–0.76; *P*<0.001). The best cut-off value of TLA/AA for predicting the occurrence of MR in patients with AF was 1.38 with sensitivity 93.5% and specificity 85.7% (Figure 4).

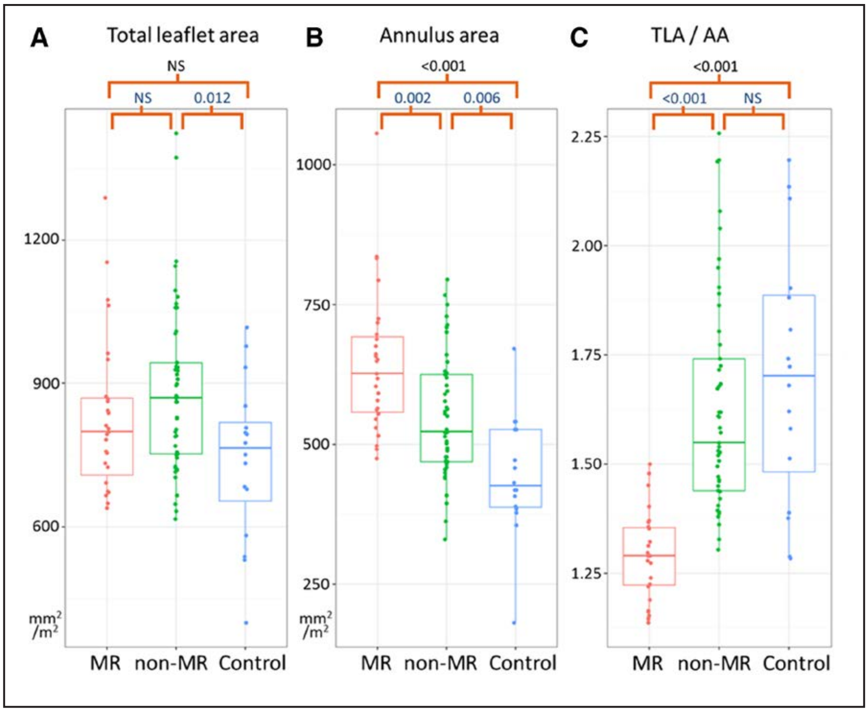

Figure 2. Overlaps in parameters among the 3 groups. In annulus area (**A**) and total leaflet area (**B**), there were significant overlaps among 3 groups, and it was difficult to distinguish the groups based on these parameters. However, TLA/AA had much less overlap among the groups (**C**). MR indicates mitral regurgitation; NS, not significant; and TLA/AA, the ratio of total leaflet area/annulus area.

Table 3 shows the results of multivariable analysis. Even after adjustment by a multivariable regression model using the previously reported risk factors of MR in patients with AF including annular area,[5,21] TLA/AA was independently and significantly associated with significant MR (odds ratio, 0.76 per %; 95% CI, 0.65–0.89 per %; P<0.001), while AA was not (odds ratio, 0.54 per cm²; 95% CI, 0.19–1.56 per cm²; P=0.26). The stability of the multivariable model was appropriate with all the variance inflation factors between 1.4 and 2.5, suggesting that there was no multicollinearity problem and this model is appropriate.[23]

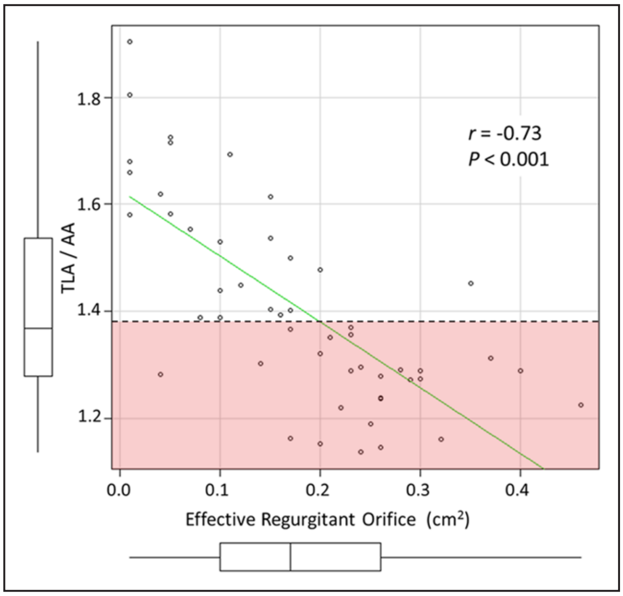

Figure 3. Correlation between TLA/AA and effective regurgitant orifice. In linear regression analysis, TLA/AA was significantly and inversely associated with effective regurgitant orifice (r=−0.73, P<0.001). TLA/AA indicates the ratio of total leaflet area/annulus area.

Discussion

In this study, we analyzed detailed 3D TEE parameters of mitral valve in patients with AF. We successfully showed that (1) there was a significant difference in the degree of leaflet remodeling between AF patients with and without MR; (2) TLA/AA, an index of leaflet remodeling, was significantly and inversely associated with effective regurgitant orifice of MR; (3) TLA/AA was superior in predicting the occurrence

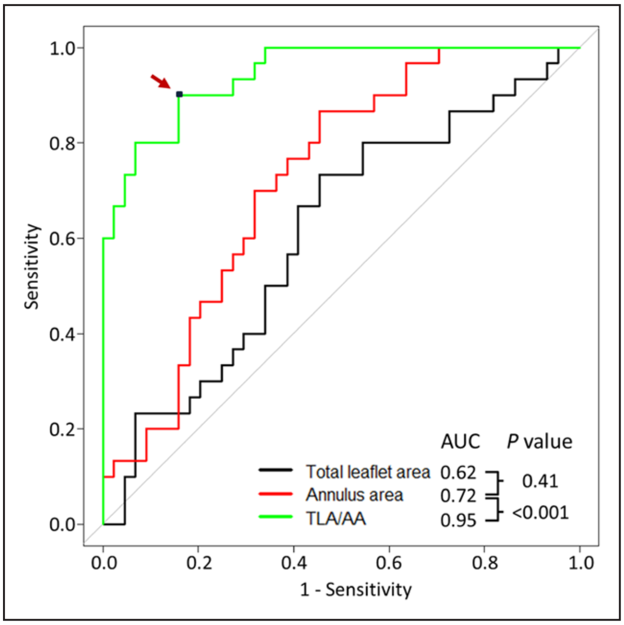

Figure 4. Receiver-operating characteristics (ROC) curve for the occurrence of mitral regurgitation (MR) in patients with atrial fibrillation (AF). ROC curve analysis showed that area under the curve (AUC) of TLA/AA was significantly higher than that of annulus area or total leaflet area. The best cut-off value of TLA/AA for predicting the occurrence of significant MR in patients with AF (arrow) was 1.38 with sensitivity 93.5% and specificity 85.7%. TLA/AA indicates the ratio of total leaflet area/annulus area.

Table 3. Multivariate Analysis

	OR (95% CI)	*P* value
LA volume index, per cm²	1.12 (1.03–1.22)	0.01
Persistent AF	0.25 (0.03–2.18)	0.21
Annular area, per cm²	0.54 (0.19–1.56)	0.26
TLA/AA, per %	0.76 (0.65–0.89)	<0.001

Multivariate regression model was constructed using previously reported risk factors of mitral regurgitation (MR) in patients with atrial fibrillation (AF), including annulus area. Total leaflet area/annulus area (TLA/AA) was independently and significantly associated with significant MR, while annulus area was not. The stability of the multivariate model was appropriate with all the variance inflation factor below 2.0 (1.01–1.06), suggesting there was no multicollinearity problem and this model is appropriate. CI indicates confidence interval; LA, left atrium; and OR, odds ratio.

of significant MR in patients with AF over crude AA or TLA; and (4) TLA/AA was significantly associated with the occurrence of MR in patients with AF even after adjustment by previously reported risk factors including AA.

AF is one of the most common cardiac rhythm disorders, which begets LA enlargement and succeeds annular dilatation.[1,2,5] The relationship between annular dilatation associated with AF and MR remains controversial. Although previous studies reported that isolated annular dilatation does not typically cause important MR,[3,24] recent studies consequently showed the presence of MR associated with AF and succeeding annular dilatation.[4–6] In clinical practice, we occasionally encounter AF patients with moderate or severe MR. Most of them have a certain level of annular dilatation; however, we found that among the patients with similarly enlarged annuluses, MR prevalence varies. Typical cases are shown in Figure 5. These two cases have similarly enlarged mitral annulus. However, in this case A, who has no MR, the TLA was 1109 mm2/m², which is significantly larger than the mean value of the leaflet area in normal subjects (more than +2 SD; 741±169 mm²/m²). This suggests that in this case A, although the mitral annulus was enlarged, the sufficient leaflet remodeling prevent significant MR.

In functional MR, leaflet remodeling/enlargement has been reported as a compensating mechanism for the dilated mitral annulus and tethering of the mitral valve because of LV dilatation.[8,9] Chaput et al[8] elegantly demonstrated that the development of significant functional MR in patients with LV dysfunction is associated with insufficient leaflet remodeling. Ring et al[6] previously showed that in patients with MR associated with AF, coaptation index (coaptation area divided by TLA) was reduced and in patients with functional MR when compared with normal subjects. However, to the best of our knowledge, there has been no study comparing the degree of leaflet remodeling between AF patients with varied MR prevalence.

In a previous report performed to investigate the determinants of the leaflet remodeling in the functional MR, the annulus size had the strongest correlation with the degree of the leaflet elongation (r^2=0.87).[9] Similarly, in our current study, the correlation between the leaflet area and the AA was strong in the patients with MR as well (r^2=0.85). Therefore, comparison of the crude leaflet area between the groups with the different annulus size does not represent the degree of leaflet remodeling precisely. In other words, if the degree of the leaflet remodeling

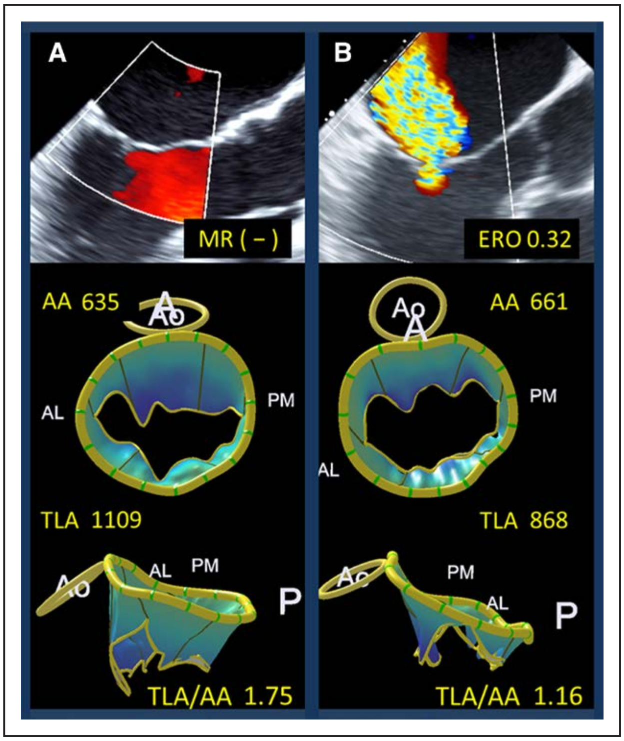

Figure 5. Three-dimensional model of the patient with and without mitral regurgitation (MR). The patient A had no MR and the patient B had significant MR (ERO=0.32 cm²). Although these patients had similarly enlarged annulus (A, 635 vs B, 661 mm²/m²), total leaflet area was rather different (A, 1109 vs B, 868 mm²/m²). As a result, total leaflet area/annulus area (TLA/AA) of the patient A was 1.75, while that of B was 1.16, indicating insufficient leaflet remodeling. AA indicates annulus area; and ERO, effective regurgitant orifice.

is the same in the MR and non-MR groups, the leaflet area must be larger in the MR group. Accordingly, we used TLA/AA as the index of the degree of the leaflet remodeling.

In this study, there were significant overlaps in the AA between AF patients with varied MR prevalence, whereas TLA/AA was clearly different between groups. Moreover, receiver-operating characteristics analysis showed that the area under the curve of TLA/AA was significantly superior to that of AA. These findings suggest that a small TLA/AA, reflecting insufficient leaflet remodeling to annular dilatation, rather than crude annular dilatation plays a crucial role in the occurrence of MR. Multivariable analysis revealed that the TLA/AA, and not the AA, was independently associated with significant MR.

Leaflet remodeling in functional MR has been reported to be due not only to passive stretch but also to active enlargement of the mitral valve tissue. Dal-Bianco et al[17] reported that mechanical stresses imposed by tethering increased the mitral valve leaflet area by 17%. They reported that endothelial–mesenchymal transdifferentiation is the main mechanism of leaflet remodeling in functional MR, as leaflet thickness also increased to 2.8 times. However, in our results, leaflet thickness was not different between patients with AF and control subjects. In the setting of MR in patients with AF, because there is no force to tether leaflets toward the apex, the mechanism may be different from that of functional MR due to LV dysfunction. One possible mechanism may be association with LA and mitral annular dilatation. It is established that in both healthy and pathological state, such as fetal to adulthood growth[25] and pathological LV, LA and mitral annular dilatation,[8,9] the mitral leaflet grows and enlarges proportionally to the mitral annular enlargement. In the patients with AF, the mitral leaflet may grow by the similar mechanisms to that of the LA and mitral annular dilatation. However, because we have no data about pathology, further studies are warranted to discover the mechanisms for such leaflet remodeling.

In our study, the severity of MR was moderate in most patients in the MR group, while mean vena contracta width was 5.1±1.0 mm. Kihara et al[4] reported that among 18,695 open heart surgery patients, there were only 12 with an indication for surgery due to their MR with AF. However, we believe that MR in patients with AF cannot be neglected, as the number of patients with AF is increasing. By 2050, the number of patients in the United States with AF will be ≈10 million.[26,27] In addition, AF is associated with a 3-fold increased risk of incident heart failure, and many studies have reported that, in patients with heart failure, even moderate functional MR affects the prognosis.[7,28–30] Therefore, MR in patients with AF has potential to influence the prognosis of several patients, and should undoubtedly be studied in the future.

Study Limitations

This study had some limitations. First, this was a single-center retrospective observational study, including relatively small number of patients. Second, we used TEE images to analyze detailed morphology of the mitral valve. TEE is one of the best modalities to observe the mitral valve in vivo; however, because of its discomfort, TEE requires sedation. Previous studies showed that general anesthesia reduced the severity of functional MR due to LV dilatation.[31,32] However, in our study, the sedation was mild enough for most patients to be able to stop breathing. Because the reduction of MR severity has been reported associated with the depth of anesthesia,[32] the influence of the sedation in our study might be much smaller than in those studies. Finally, 2D proximal isovelocity surface area and vena contracta width might underestimate the severity of MR because functional MR tends to have elliptical orifice. However, in functional MR, the radius of proximal isovelocity surface area and vena contracta width dynamically change through systole and we measured the largest radius as previously described.[33] It might overestimate the severity of MR. In between these under- and overestimation, the severity of MR may be near appropriate at some level. In fact, these methods have been consistently used in functional MR and in degenerative MR and successfully predicted the prognosis of patients with functional MR.[7,34,35] Guidelines also recommend these methods and integrated evaluation using these methods.[15,18,36] In addition, the correlation between 3D vena contracta area, which may overcome the concern associated with elliptical orifice, and integrated 2D method (r=0.88)[37] or 2D proximal isovelocity surface area alone (r=0.93, bias of effective regurgitant orifice 0.07±0.01 cm2)[38] were reported to be good.

Conclusions

In patients with AF, a small TLA/AA, an indicator of insufficient leaflet remodeling, is strongly associated with significant MR. These results suggest that leaflet remodeling plays a crucial role in the occurrence of MR in patients with AF. Further studies are needed to investigate the mechanisms of leaflet remodeling in patients with AF and the prognostic impact of MR in patients with AF.

Disclosures

None.

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CLINICAL PERSPECTIVE

With the increased use of radio-frequency catheter ablation techniques for atrial fibrillation, echocardiography has become an important preprocedural evaluation and not infrequently patients are encountered with mitral regurgitation (MR) without left ventricular dysfunction/dilatation. It remains unclear whether annular dilatation is the main contributor of MR in these patients. In this study, we showed that the insufficient leaflet remodeling relative to the dilated annulus, rather than crude annular dilatation, is the main contributor to MR. We showed that the patients with atrial fibrillation had significantly larger mitral valve leaflets than control subjects. In the patients with significant MR, total leaflet area/annulus area ratio, an index of the leaflet remodeling versus dilated mitral annulus, was much smaller (1.29±0.10) than control subjects, whereas patients without MR had similar total leaflet area/annulus area ratio (1.65±0.24) to control subjects (1.70±0.29). Moreover, total leaflet area/annulus area ratio was inversely correlated to the severity of MR and was independently associated with significant MR. With the aging of the population, there are more patients with atrial fibrillation and understanding the mechanism of MR in these patients will help to stratify these patients and provide potential therapeutic strategies.

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Insufficient Leaflet Remodeling in Patients With Atrial Fibrillation: Association With the Severity of Mitral Regurgitation

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