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Relationship between geometric changes in mitral annular/leaflets and mitral regurgitation in patients with atrial fibrillation

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Abstract

The objective of the study was to determine the geometric changes in mitral annular and/or leaflets spatial conformation in patients with atrial fibrillation (AF) complicated with severe atrial mitral regurgitation (AMR) by using real-time 3-dimensional transesophageal echocardiography, aiming to explore whether this condition could be improved through self-modulation of mitral annulus and/or leaflets after the restoration of sinus rhythm.

Fifty-five patients who were diagnosed with AMR and subject to 1-year follow-up were recruited in this clinical trial. All patients successfully received AF ablation. The intercommissural and anteroposterior diameter, annular height, mitral valve area (MVA), tenting height and volume, annular spherical index, fractional area change of MVA (MVA-FAC), and coaptation index (CP-I) were defined and measured by mitral-valve quantification software. Left ventricular size and function, maximum LA volume (LAV), and LA dimensions were equally recorded.

During 1-year follow-up, AMR was significantly decreased in patients with sinus rhythm ($P<0.001$). CP-I, MVA-FAC, and LAV index were independently associated with the reduction of AMR.

AMR can be improved through the recovery of LAV after ablation, which probably affects the configuration of the annular space and the coaptation of the leaflets.

Abbreviations: AF = atrial fibrillation, AMR = atrial mitral regurgitation, AP = anteroposterior, ASI = annular spherical index, CP-I = coaptation index, EROA = effective regurgitant orifice area, FMR = functional mitral regurgitation, IC = intercommissural, LA = left atrial, LAV = left atrial volume, LAV-I = LAV index, LV = left ventricular, MVA = mitral valve area, MVA-FAC = fractional area change of MVA, MVQ = mitral-valve quantification, PV = pulmonary vein, RT-3D TEE = real-time 3-dimensional transesophageal echocardiography, TH = tenting height, TV = tenting volume.

Keywords: 3-dimensional transesophageal echocardiography, atrial fibrillation, atrial function, mitral regurgitation

1. Introduction

Previous studies have demonstrated that the dominant mechanism underlying functional mitral regurgitation (FMR), especially in patients with left ventricular (LV) dysfunction, is the failure of optimal coaptation of the mitral valve leaflets owing to the displacement of sub-valvular apparatus.[1–6] Recent investigations have emphasized the importance of atrial fibrillation (AF) as the main cause of atrial mitral regurgitation (AMR).[7,8] However, of the relationship between the geometric changes of the mitral annular, leaflets, and the incidence of AMR, as well as whether it can be improved after successful recovery of sinus remain to be further elucidated.

The advent of real-time 3-dimensional transesophageal echocardiography (RT-3D TEE) has made it possible to visualize the entire spatial configuration of the annular and leaflets compared with traditional 2-dimensional echocardiography.[10] In animal models with FMR, the development of valvular insufficiency has been predicted. Compared with traditional 2-dimensional echocardiography, RT-3D TEE has been proven to be advantageous in the visualization of the leaflet configuration.

In this study, RT-3D TEE was applied to determine the geometric changes of the spatial conformation of the mitral annular and leaflets in patients with AF who were complicated with evident AMR after successful ablation. During 1-year follow-up, whether this condition could be improved through self-modulation of mitral annulus and/or leaflets after the restoration of sinus rhythm was investigated by monitoring the variations in the atrial volume.

2. Materials and methods

2.1. Study subjects

All patients who were diagnosed with AF which was not controlled with medication and received catheter ablation between January 2012 and November 2015 were eligible for the inclusion criteria. Among them, patients with secondary AMR of at least moderate severity who also had completed 1-year follow-up after ablation were eventually recruited in this MR cohort. The clinical AF

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syndrome was determined based on the predominant arrhythmia at the time of inclusion and defined as paroxysmal if AF episodes self-terminated within 7 days and defined as persistent if typical AF episodes lasted for 7 days or longer and/or required intervention for termination. The study procedures were approved by the Ethics Review Board of our hospital. Written informed consents were obtained from all patients.

2.2. Routine transthoracic echocardiography

Routine transthoracic echocardiography was performed before catheter ablation. Images were acquired using an iE33 unit equipped with S5-1 (Philips Medical Systems, NA, Bothell, WA). To avoid interference, patients whose MR might be due to ventricular functional MR, LV dysfunction, or morphologic mitral lesions were excluded if they had any of the follows: large LV size with ejection fraction (EF) <50%; regional wall motion abnormalities due to previous or recent myocardial infarction; clinical and echocardiographic evidence of anatomic mitral valve prolapse or stenosis. other cardiac diseases, such as congenital defects, aortic valve disease, or pericardial disease. To assess the severity of MR, MR volume and effective regurgitant orifice area (EROA) were calculated using the volumetric method.[11] MR volume was calculated as the difference between the mitral filling and aortic ejection volume and EROA as MR volume divided by the time-velocity integral of MR flow. Basic echocardiographic measurements were fulfilled and data recorded before interventional treatment for AF and during follow-up. From the parasternal long-axis view, LV end-diastolic/end-systolic diameters (LVIDd and LVIDs) and the left atrial (LA) diameter from anterior to posterior wall (LA-D) were recorded. From the apical views, the LA volume (LAV), LAV index (LAV-I), LAA, and LV EF were determined using Simpson biplane method. The mean value was calculated from at least 6 to 8 consecutive cardiac cycles, as illustrated in Table 1.

2.3. Transesophageal 3-dimensional echocardiography

The 3D-TEE was performed using a Philips iE33 unit equipped with an X7-2t transducer (Philips Medical Systems, NA). Before ablation and during follow-up, 3D data sets were acquired and analyzed in the 3D-zoom mode according to current guidelines.[12] All images were acquired at the mid-esophageal level. Sector width, depth, and gain settings were modulated to ensure that the entire mitral valve annulus was included (8-fps frame rate) and to guarantee the mitral-valve quantification (MVQ).

2.4. Mitral-valve quantification

At least 5 consecutive beats were acquired and the data sets were analyzed offline using the software designed for MVQ (Q-Lab working station; Philips Medical Systems, NA). First, the end-systolic frame, defined as the last frame prior to mitral valve opening, was selected. The intercommissural (IC) and anteroposterior (AP) diameter were manually determined and the hinge points of the leaflets in 8 rotational planes were subsequently defined before the leaflets were traced in parallel slices across the valve. Finally, the early systolic frame, defined as the 1st frame in which the mitral leaflets coapt was selected, and the previously described procedure was repeated. The mitral valve area (MVA) and total leaflet surface area in the early systole were recorded (Fig. 1). To determine whether annular function and coaptation of the mitral valve exerted an effect on AMR, several vital parameters were defined and measured according to the dedicated MVQ software as follows:

1. Mitral annular parameters: AP and IC diameter; annular height and MVA; leaflet geometry, including tenting height (TH) and tenting volume (TV).
2. Other parameters: annular spherical index (ASI) calculated as annular height to IC ratio (representing the nonplanarity of the mitral annulus, which is independent both of annular size and body surface area); fractional area change of MVA (MVA-FAC): (MVA late systole−MVA early systole)/MVA late systole × 100%; coaptation index (CP-I)[10]: (Leaflet surface area early systole−Leaflet surface area late systole)/Leaflet surface area early systole × 100%, which was indexed to the valvular size and the 3-dimensional coaptation surface area was evaluated to assess the coaptation free from body surface area.

2.5. Ablation procedures and follow-up

All patients underwent proximal atrial pulmonary vein (PV) isolation guided by circular multipolar electrode catheter recordings and elimination of all provocable PV triggers and all non-PV triggers resulting in AF, as previously described.[13] All 4 PVs were isolated routinely in patients with a medical history of persistent AF. The ablation endpoint was both persistent PV isolation and no AF with repeated incremental infusion of up to 20 μg/min of isoproterenol. Patients with identified macro reentrant atrial tachycardias had the circuit defined with the use of activation and/or entrainment mapping to guide the appropriate linear ablation strategy with an endpoint of bidirectional block.

Table 1

Basic echocardiographic measurement between 2 groups.

	Sinus rhythm (n = 34)			Recurrence (n = 21)		
	Initial	1 yr	*P*	Initial	1 yr	*P*
LA-D, cm	4.61 ± 0.38	4.25 ± 0.45	NS	4.75 ± 0.67*	4.58 ± 0.52*	NS
LAA, cm^2	22.7 ± 3.34	18.8 ± 3.45	<.05	23.3 ± 6.8*	22.1 ± 5.7*	NS
LAV, cm^3	52.77 ± 5.41	45.22 ± 6.49	<.05	55.7 ± 18.2*	51.9 ± 17.5*	NS
LAV-I, cm^3/m^2	26.30 ± 3.12	22.98 ± 3.03	<.05	29.9 ± 7.9*	27.4 ± 8.2*	NS
EF (Simpson, %)	59.2 ± 11.2	60.4 ± 12.3	NS	58.9 ± 10.4	59.4 ± 9.6	NS
LVEDD, cm	5.2 ± 0.31	5.1 ± 0.29	NS	5.3 ± 0.28	5.2 ± 0.30	NS
LVEDS, cm	3.3 ± 0.24	3.2 ± 0.22	NS	3.4 ± 0.28	3.2 ± 0.24	NS
EROA, cm^2	0.27 ± 0.03	0.21 ± 0.04	<.001	0.28 ± 0.03	0.26 ± 0.04	NS

EF = ejection fraction, EROA = effective regurgitant orifice area, LAA = LA area, LA-D = left atrial diameter, LAV = left atrial volume, LAV-I = LAV index, LVEDD = left ventricular end-diastolic dimension, LVEDS = left ventricular end systolic dimension.

* $P < .05$ represents comparison between the recurrence and sinus groups under the same conditions.

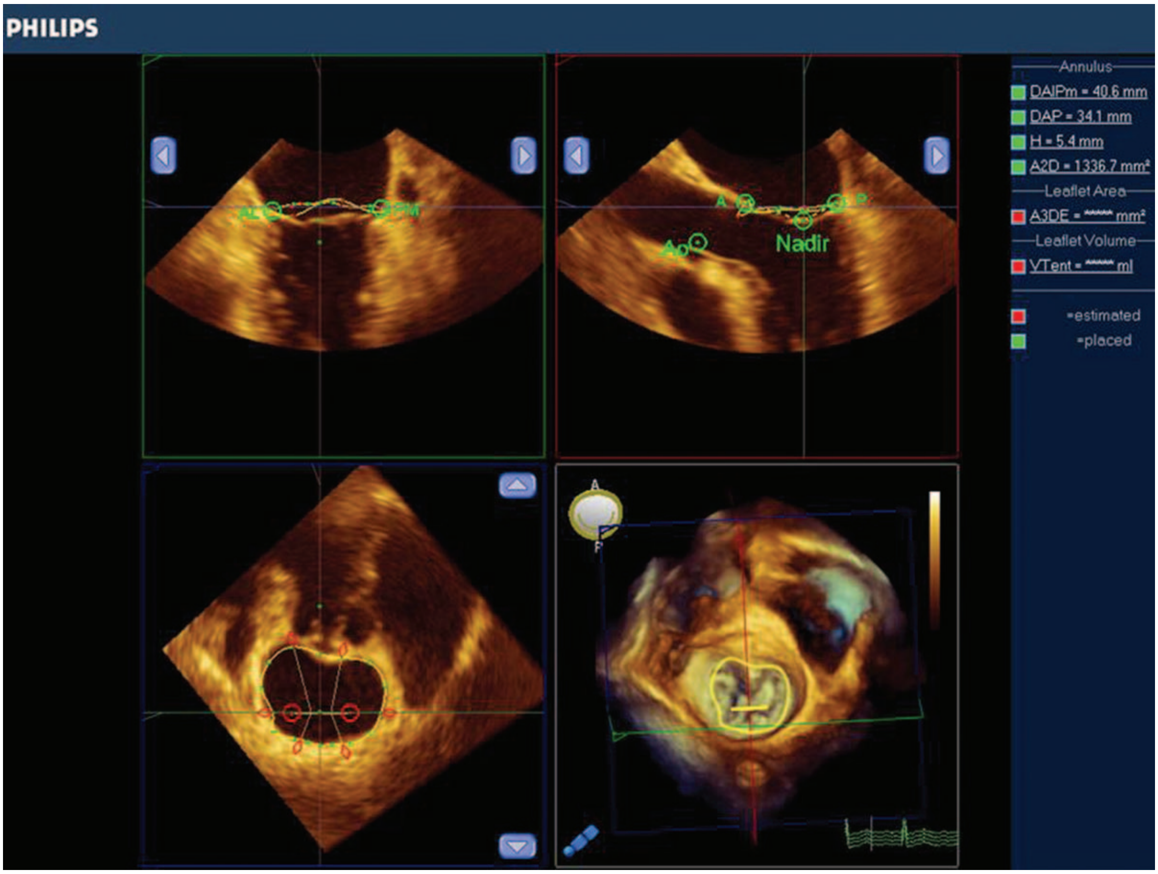

Figure 1. Mitral-valve quantification (MVQ) analysis image. The mitral annulus is displayed in 3 orthogonal planes, with the 3-dimensional (3D) image to aid orientation (bottom right pane). The values for annular parameters are displayed on the right, including intercommissural diameter (DAIP), anteroposterior diameter (DAP), annular height (H), annular area (A2D), total leaflet surface area (A3DE), tenting volume (VTent), and tenting height (HTent). To determine the coaptation index, the analysis was performed in early systole (displayed here) and repeated in end systole.

Patients were routinely medicated with antiarrhythmic medications (usually a class 1C agent or sotalol) prior to discharge. They were clinically assessed as outpatients at 3 months, 6 months, and 1 year. Symptoms, 12-lead electrocardiograms, and transthoracic echocardiograms were recorded and/or performed during each follow-up visit at the treating physician's discretion. The first 3 months after ablation were investigated at follow-up to assess for recurrence; antiarrhythmic medications were typically discontinued at 3 months if patients had paroxysmal AF and at 6 months if they had persistent AF. However, medications were continued beyond this point in selected patients based on doctor and/or patient preference even in the absence of an arrhythmia event. One-year AF recurrence was defined according to consensus guidelines as any documented electrocardiographic episode of atrial arrhythmia lasting 30 seconds or longer with or without symptoms.[14] The transthoracic echocardiography procedure previously mentioned was repeated at 1 year in selected patients.

2.6. Statistical analysis

Data were analyzed using SPSS 19.0 (SPSS, Inc, Chicago, IL) and values were expressed as mean ± standard deviation (SD). Continuous variables were presented as mean ± SD, comparing within- and between-group data were statistically analyzed using Student *t* test. Associations between mitral 3D parameters and AMR or LA function were determined by linear regression analysis. Multivariate regression analysis was employed to determine mitral annular function and coaptation factors predictive of AMR. Intra- and inter-observer variability was described by the coefficient of variation, and 95% limits of agreement of the absolute values were calculated by Bland–Altman analysis. *P* values of <.05 were considered statistically significant.

3. Results

3.1. Patient selection

A total of 479 patients underwent AF ablation at our institution between January 2012 and November 2015. Among them, 76 developed significant AMR according to EROA without an apparent primary leaflet lesion. Of these 76 patients, 55 completed their 1-year clinical follow-up, 317 days after ablation on average, were included into the AMR cohort. According to the rhythm status defined above, 34 patients were diagnosed with sinus rhythm and 21 recurred during the final follow-up.

3.2. Demographic data

A total of 55 patients were recruited in this study, 30 males and 25 females. The mean age of all patients was (64 ± 12) years. Among them, 14 patients were complicated with diabetes mellitus (25.5%), 34 cases were diagnosed with systemic hypertension (61.8%), and 26 patients were complicated with hypercholesterolemia (47.3%), respectively.

3.3. Basic echocardiographic measurement

Basic echocardiographic measurement of AMR is illustrated in Table 1. After 1-year follow-up, AMR was significantly decreased in patients with sinus rhythm (EROA: 0.27 ± 0.03 vs $0.21 \pm 0.04\,cm^2$, $P < .001$). No changes were observed in recurrent patients. After 1-year follow-up, the LA area (LAA) and volume in patients with sinus rhythm was significantly decreased compared with the values before ablation (LAA: 22.7 ± 3.34 vs $18.8 \pm 3.45\,cm^2$, LAV: 52.77 ± 5.41 vs 45.22 ± 6.49, LAV-I: 26.30 ± 3.12 vs 22. 98 ± 3.03, all $P < .001$), whereas no changes were noted in recurrent patients. In both groups, normal LV size and systolic function were not significantly changed during 1-year follow-up.

3.4. 3D annular and leaflets parameters

Despite normal LV size and systolic function were unchanged, the MVA was enlarged in patients with AMR, whereas it was considerably decreased after 1-year follow-up in those in sinus rhythm after ablation (13.22 ± 1.27 vs $10.36 \pm 1.33\,cm^2$, $P < .001$). Both AP and IC values were significantly reduced after 1-year follow-up in patients with sinus rhythm (AP: 30.76 ± 3.58 vs 26.26 ± 3.23, IC: 40.15 ± 3.03 vs 34.62 ± 2.45, both $P < .001$). At 1 year after ablation, the fractional MVA change was improved, followed by a decreased MVA in patients with sinus rhythm (6.11 ± 0.72 vs $7.76 \pm 0.86\%$, $P < .001$), which evidently increased the leaflets coaptation (CP-I: 9.30 ± 1.29 vs 11.32 ± 1.52, $P < .001$). Conversely, all parameters described above did not significantly differ in recurrent patents (Table 2).

3.5. Reproducibility of 3D measurement

Measurement variability for intra-observer differences was described as follows: mitral annular area = 3.2% + 0.6 cm^2; TH = 3.6% + 0.5 mm; TV = 4.6% + 0.4 mL; leaflet surface area = 3.3% + 0.9 cm^2; and CP-I = 5.4 + 2.1%. Inter-observer differences were as follows: mitral annular area = 4.9% + 1.1 cm^2; TH = 7.5% + 1.1 mm; TV = 6.7% + 0.8 mL; leaflet surface area = 5.3% + 1.1 cm^2 and CP-I = 6.8 + 2.6%.

3.6. Linear regression analysis

At 1 year after ablation, linear regression analysis in the sinus rhythm patients was performed to investigate the independent association between the changes in AMR, annular function, and coaptation ability. The reduction in EROA at 1 year after ablation was strongly associated with the CP-I changes ($r = -0.78$, $P < .001$) and MVA-FAC ($r = -0.72$, $P < .001$). Apart from these, the changes in CP-I and MVA-FAC were also well correlated ($r = 0.71$, $P < .001$). The reduction in LAV-I was also associated with changes in CP-I ($r = -0.75$, $P < .001$) and MVA-FAC ($r = -0.69$, $P < .001$) (Figs. 2–6). After multivariate analysis, the changes in CP-I ($\beta = -0.549$, $P < .05$), MVA-FAC ($\beta = -0.309$, $P < .05$), and LAV-I ($\beta = 1.712$, $P < .05$) were independently associated with the reduction in EROA (Table 3).

4. Discussion

The mechanisms and related factors of FMR have been well described in several prospective studies.[15–18] Global or regional LV function contributes to changes in the configuration of the mitral annulus, which produce obvious FMR.[19,20] However, recent studies focusing on the impact of MR on the atrium suggest that AF can lead to secondary MR with normal leaflet motion, known as AMR, which is improved along with the restoration of sinus rhythm.[8,9] To our best knowledge, there have been no prospective data that could provide quantitative evidence of the association between the LA volumetric variation and the severity of AMR, which probably results from of the changes in the steric configurations of the mitral annulus and/or leaflets before and after sinus rhythm is restored in patients with AF.

One of the greatest advantages of 3D-TEE over traditional 2-dimensional techniques for evaluating mitral-valve structure is that it provides concurrent access to the spatial parameters of both annular and leaflets, such as AP and IC diameter and annular height and area, etc. Several studies have demonstrated the generation of these parameters by MVQ from 3D-TEE is feasible in normal subjects and patients.[10,21]

Table 2

Mitral 3-dimesional parameters between 2 groups.

	Sinus rhythm (n=34)			Recurrence (n=21)		
	Initial	1 yr	*P*	Initial	1 yr	*P*
Annular parameter						
MVA, cm^2	13.22±1.27	10.36±1.33	<.001	13.68±1.58	13.50±1.59*	NS
AP	30.76±3.58	26.26±3.23	<.001	32.90±3.0*	31.43±3.11*	NS
IC	40.15±3.03	34.62±2.45	<.001	41.23±3.45	39.86±2.67*	NS
AH, mm	5.98±0.50	5.74±0.51	NS	6.04±0.49	5.83±0.50	NS
ASI, %	14.9±1.6	16.2±1.9	NS	14.7±1.7	14.5±1.4	NS
Leaflet parameter						
TH, mm	3.71±0.82	3.85±0.86	<.001	3.47±0.62*	3.55±0.56*	NS
TV, mL	1.65±0.39	1.62±0.33	NS	1.61±0.38	1.63±0.32	NS
MVA-FAC, %	6.11±0.72	7.76±0.86	<.001	6.68±0.78*	6.49±0.70*	NS
CP-I, %	9.30±1.29	11.32±1.52	<.001	8.87±0.99*	8.76±0.94*	NS

AH = annular height, AP = anteroposterior, ASI = annular spherical index, CP-I = coaptation index, IC = intercommissural, MVA = mitral valve area, MVA-FAC = fractional area change of mitral valve area, TH = tenting height, TV = tenting volume.

* $P < .05$ denotes comparison between the recurrence and sinus groups under the same conditions.

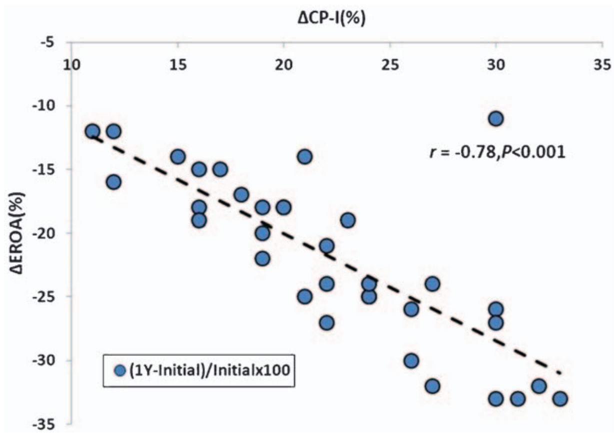

Figure 2. Scatterplot showing the correlation between changes of coaptation index (ΔCP-I) and effective regurgitant orifice area (ΔEROA) in patients with sinus rhythm before ablation and after 1-year follow-up.

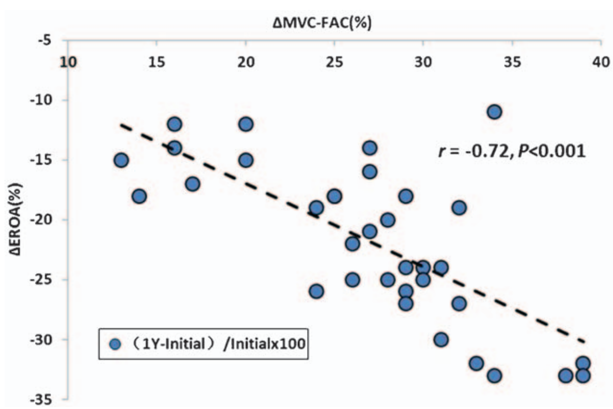

Figure 3. Scatterplot showing the correlation between changes of fractional area change of mitral valve area (ΔMVA-FAC) and effective regurgitant orifice area (ΔEROA) in patients with sinus rhythm before ablation and after 1-year follow-up.

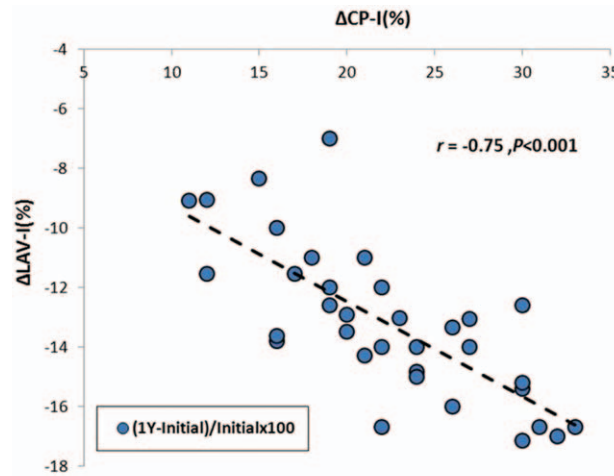

Figure 5. Scatterplot illustrating the correlation between left atrial volume index (ΔLAV-I) and coaptation index (ΔCP-I) in patients with sinus rhythm before ablation and after 1-year follow-up.

In current investigation, the functional–anatomical changes of the mitral leaflets and annulus in patients with AF with relatively obvious AMR after an ablation procedure were characterized using 3D-TEE. During nearly 1 year after sinus-rhythm reconstruction in patients with sustained sinus rhythm, the fractional MVA change was improved, followed by decreased MVA, which increased the leaflets' CP. This was the most clearly manifested by the strong association between the changes in EROA, CP-I, and fractional MVA. In previous animal models, the concept of CP-I was introduced to describe the ability/loss of coaptation of the mitral leaflets in patients with FMR.[10] In our study, the application of this index to individuals with AF and obvious AMR confirm the mechanism of regurgitation to be loss of coaptation, presumably as a consequence of impaired annular fractional change.[21]

Furthermore, we also found that the reduction in the LAV was associated with the changes in CP-I and fractional MVA in patients with sinus rhythm. After multivariate analysis, the changes in CP-I and fractional MVA and the LAV-I were

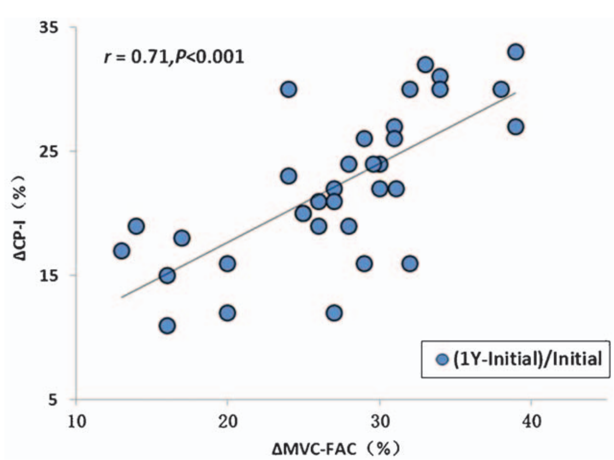

Figure 4. Scatterplot illustrating the correlation between fractional area change of mitral valve area (ΔMVA-FAC) and coaptation index (ΔCP-I) in patients with sinus rhythm before ablation and after 1-year follow-up.

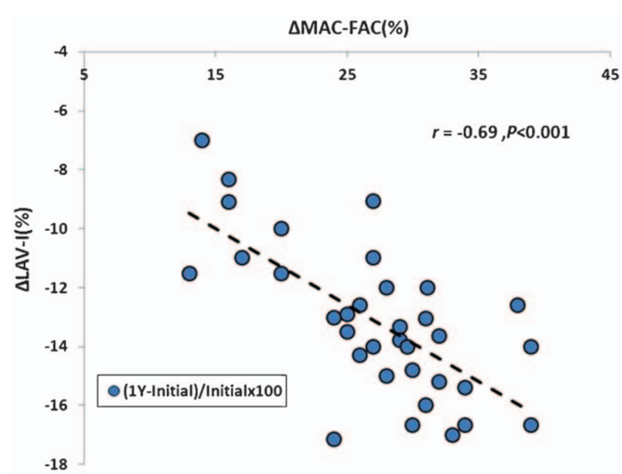

Figure 6. Scatterplot illustrating the correlation between left atrial volume index (ΔLAV-I) and mitral valve area (ΔMVA-FAC) in patients with sinus rhythm before ablation and after 1-year follow-up.

Table 3

Multivariate association between related parameters and AMR changes after 1-year follow-up.

	Dependent variables		
	Effective regurgitant orifice area* (n=34)		
	β	95 CI %	P
Annular parameter			
MVA, cm2*	−0.323	−0.712 to 0.031	.072
AP-Diam*	0.244	−0.084 to 0.572	.139
IC-Diam*	2.755	−6.669 to 12.179	.555
Annu-H, mm*	−2.746	−10.215 to 5.724	.513
ASI, %*	2.625	−4.668 to 9.917	.468
Leaflet parameter			
TH, mm*	0.013	−0.063 to 0.090	.73
TV, mL*	−0.021	−0.110 to 0.068	.63
MVA-FAC, %*	−0.309	−0.626 to 0.018	.041
CP-I, %*	−0.606	−0.958 to 0.253	.001
LA parameters			
LAV, cm3*	0.349	0.050–0.649	.024
LAV-I, cm3/m2*	1.712	1.002–2.442	.000
LAA, cm2*	0.011	−0.188 to 0.211	.909
LAD, cm*	−0.070	−0.428 to 0.288	.694

AMR=atrial mitral regurgitation, Annu-H=annular height, AP-Diam=anteroposterior diameter, ASI=annular spherical index, CP-I=coaptation index, EROA=effective regurgitant orifice area, IC-Diam=intercommissural diameter, LAA=LA area, LAD=LA diameter, LAV=left atrial volume, LAV-I=LAV index, MVA=mitral valve area, MVA-FAC=fractional area change of MVA, TH=tenting height, TV=tenting volume.

* Mean changes in all corresponding parameters before ablation and after 1-year follow-up.

independently associated with the reduction of MR, suggesting that MR was decreased along with improved coaptation of the leaflets, which is probably relevant to the reduced mitral annular fractional changes followed by the decrease in LAV. An important conclusion from this result is that after a relatively long follow-up of patients with AF with AMR who have undergone sinus rhythm reconstruction, the improvement in the LAV appears to be the key factor in improving mitral annular size and leaflet coaptation. Many researchers have demonstrated that displacement of the subvalvular apparatus, especially the tenting area and/or volume, plays a vital role in FMR due to LV dysfunction.[22,23] Consequently, except for improving global or regional LV function, the surgical treatment to FMR other than restrictive annuloplasty constantly involves with a comprehensive design to restore normal subvalvular geometry.[2,24,25] Unlike the case with FMR due to LV dysfunction, the restoration of sinus rhythm can reduce AMR in patients with AF after successful ablation, also decreasing the mitral annular size and increasing the leaflet coaptation, followed by improvement in LA volume or size. Our findings suggest the wide range of sinus rhythm reconstruction should be implemented among in patients with AF complicated with severe AMR. Therefore, it is important to recognize AMR among patients with AF as a distinct entity with a characteristic mitral annular geometry that requires a unique approach to its management.

5. Conclusion

To conclude, RT-3D TEE was adopted to determine the degree of self-improvement after 1-year follow-up in patients with AF complicated with AMR, aiming to investigate evaluate the clinical efficacy of the interventions in the treatment of sinus rhythm. The observed changes are modulated through the recovery of LA volume, which probably affects the configuration of the annular space and the coaptation of the leaflets.

5.1. Study limitations

There are several limitations to be acknowledged. For the evaluation of AMR, EROA with the volumetric method was employed rather than the proximal isovelocity surface area method because the geometry of the latter area in AMR is elongated, leading to underestimation of the EROA.[26] Quantification of the severity of MR in AF is problematic owing to the variability stroke volume. Besides, this is a single-center study with a limited sample size, and the conclusions drawn from this investigation remain to be validated by subsequent multi-center studies.

Author contributions

Conceptualization: Hua Li.
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Funding acquisition: Hua Li.
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Methodology: Xiaofeng Chen.
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Resources: Zhenhua Feng, Lei Song.
Software: Zhenhua Feng.
Supervision: Sha Tang.
Validation: Sha Tang.

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