Multimodality imaging to guide cardiac interventional procedures

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Comparison of left atrial volumes and function by real-time three-dimensional echocardiography in patients having catheter ablation for atrial fibrillation with persistence of sinus rhythm versus recurrent atrial fibrillation three months later

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ABSTRACT

Real-time 3-dimensional echocardiography (RT3DE) can provide a unique combination of accurate left atrium (LA) volume quantification and rapid, automatic assessment of LA function. The aim of the study was to evaluate the changes in LA volumes and function in patients with atrial fibrillation (AF) undergoing radiofrequency catheter ablation (RFCA), using RT3DE.

Fifty-seven consecutive patients referred for RFCA were studied. Paroxysmal AF was present in 43 patients (75%), and persistent AF in 14 (25%). After a mean follow-up of 7.9 ± 2.7 months, patients were divided into 2 groups: successful RFCA (SR group) and recurrence of AF (AF group). RT3DE was performed before, within 3 days and 3 months after RFCA to assess LA volumes (maximum, minimum and preA) and LA functions (passive, active and reservoir). A total of 38 patients (67%) had successful RFCA (SR group). Immediately after RFCA, no significant changes in LA volumes and function were observed. After 3 months, a significant reduction in LA volumes (maximum: from 26 ± 8 to 23 ± 7 mL/m^2, $p < 0.01$) was noted only in the SR group, together with a significant improvement in LA active (from 22 ± 8 to 33 ± 9%, $p < 0.01$) and reservoir functions (from 116 ± 45 to 152 ± 54%, $p < 0.01$). Conversely, the AF group showed a trend towards a deterioration of LA volumes and function. In conclusion, in patients who maintain sinus rhythm after RFCA, a significant reverse remodeling and functional improvement of the LA is observed using RT3DE.

INTRODUCTION

Recently, real-time 3-dimensional echocardiography (RT3DE) has been validated against magnetic resonance imaging and has been shown to be more accurate and reproducible than 2-dimensional (2D) echocardiography for the quantification of left atrial (LA) volumes (1,2). Furthermore, RT3DE may be a novel, reliable technique for the assessment of LA function, providing unique information about phasic changes of LA volumes during the cardiac cycle (3,4). In the present study, RT3DE was used to evaluate the changes in LA volumes and function in atrial fibrillation (AF) patients treated with radiofrequency catheter ablation (RFCA).

METHODS

In a 10 months period, 57 consecutive patients (44 men; age 56 ± 9 years) with symptomatic drug-refractory AF, referred to our institution for RFCA in accordance to the current guidelines criteria, were included in this study. According to the ACC/AHA/ESC Guidelines definition (5), paroxysmal AF was present in 43 patients (75%), while persistent AF was present in the remaining 14 patients (25%); none of the patients had permanent AF. Mean AF duration (calculated from the time of the first episode) was 4.6 ± 4.1 years and the patients had an unsuccessful treatment with 3 ± 1 anti-arrhythmic drugs (mainly flecainide, propafenone, sotalol and amiodarone).

After RFCA, the patients were evaluated at the out-patient clinic on a regular basis. During follow-up, all medication, including anti-arrhythmic drugs, were continued in all patients for 3 months after the RFCA procedure. Afterwards, anti-arrhythmic drugs were discontinued at discretion of the physician. At the latest follow-up, successful RFCA was defined as the absence of symptomatic recurrences lasting more than 3 minutes (6) and/or the absence of AF episodes lasting more than 30 seconds (detected with 24-hours Holter ECG recording and surface ECG) during follow-up, after a blanking period of 1 month (5,7). Accordingly, the study population was divided into 2 groups: patients with successful RFCA (SR group) and patients who had recurrence of AF (AF group).Before and within 3 days after the ablation procedure, RT3DE was performed to assess LA and left ventricular (LV) size and function. In addition, conventional 2D color-Doppler echocardiography was performed to assess mitral regurgitation (MR) and LV filling pattern. After 3 months follow-up, the echocardiograms were repeated to assess the effect of the RFCA on LA volumes and function.

Real-time 3-dimensional echocardiography

Patients were imaged with a commercially available system (iE33, Philips Medical Systems, Bothell, Washington) equipped with X3, fully sampled matrix transducer. Apical full-volume data sets were obtained in all patients, combining 7 small real-time sub-volumes to provide a

larger pyramidal volume. The acquisition was performed during end-expiratory apnea within 1 breath hold. Frame rate ranged from 20 to 35 frames/sec. The RT3DE data sets were stored digitally and quantitative analyses were performed off-line using a semi-automated contour tracing algorithm (Q-Lab, version 5.0, Philips Medical Systems) based on 5 reference points. In all patients the image quality was sufficient for quantitative analysis and the post-processing of the images was performed within 10 minutes. Left ventricular volumes and function were assessed as previously described in detail (8).

Quantification of LA volumes was performed using the semi-automated contour tracing algorithm developed for the LV, but marking 5 atrial reference points: 4 at the anterior, inferior, lateral and septal part of atrial dome and 1 at the level of the mitral annulus (Figure 1). The position of the reference points was chosen to avoid changes in the view orientation that the software automatically generates, since the position of the dome of the LA is opposite of the apex of the LV. Manual corrections of the automatic trace were made to exclude the LA appendage and the pulmonary vein ostia. Left atrial volumes were measured at 3 time points during the cardiac cycle: 1) maximum volume (LA_{max}) at end-systole, just before mitral valve opening; 2) minimum volume (LA_{min}) at end-diastole, just before mitral valve closure; 3) volume before atrial active contraction (LA_{preA}) obtained from the last frame before mitral valve reopening or

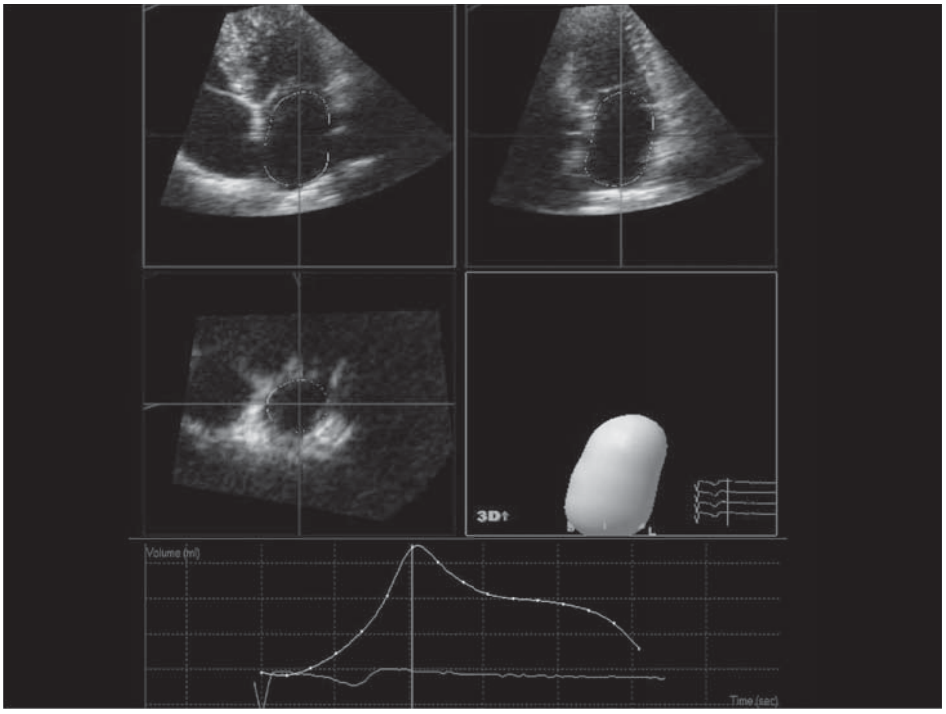

Figure 1. Assessment of LA volumes using RT3DE. An automatic border detection is obtained marking 5 reference points in the apical 2- and 4-chamber views (upper panel) and the LA 3D model is provided by the software. The changes of LA volumes during the heart cycle are plotted as a curve (lower panel).

at time of the P wave on the surface ECG. All LA volumes were indexed to the body surface area, as recommended (9).

Twenty patients were randomly identified for inter- and intra-observer agreement. According to the Bland-Altman analysis, intra-observer variability was excellent with a mean differences of 1.2 ± 2.9 mL for LA_{max}, 0.1 ± 1.1 mL for LA_{min} and 0.8 ± 2.3 mL for LA_{preA} (p = NS). Inter-observer variability was also good with a mean difference for LA_{max}, LA_{min} and LA_{preA} of 3.6 ± 5.6 mL, 0.7 ± 5.4 mL and 1.9 ± 3.4 mL, respectively (p = NS).

The LA function was derived from the LA volumes and expressed with the following parameters (10,11): 1) Total atrial emptying fraction: $LA_{EF} = ([LA_{max} - LA_{min}]/LA_{max}) \times 100$; 2) Active atrial emptying fraction: $LA_{active} = ([LA_{preA} - LA_{min}]/LA_{preA}) \times 100$, which is considered an index of LA active contraction; 3) Passive atrial emptying fraction: $LA_{passive} = ([LA_{max} - LA_{preA}]/LA_{max}) \times 100$, which is considered an index of LA conduit function; 4) Atrial expansion index: $LA_{reservoir} = ([LA_{max} - LA_{min}]/LA_{min}) \times 100$, which is considered an index of LA reservoir function.

The severity of MR was graded semi-quantitatively from color-Doppler images in the conventional parasternal long-axis and apical 4-chamber view and characterized as follows: absent, mild (ratio jet area/LA area <20%), moderate (jet area/LA area 20% to 40%) and severe (jet area/LA area >40%) (12). Left ventricular diastolic function was evaluated according to the Canadian Consensus recommendations (13) through the following Doppler measurements: ratio of early (E) to late (A) diastolic filling velocities (E/A) and deceleration time (DT) of the E wave.

Radiofrequency catheter ablation procedure

The RFCA procedure was aimed at electrical isolation of all pulmonary veins from the LA. Endocardial mapping was performed with a 4-mm quadripolar mapping/ablation catheter (7Fr Thermocool, Biosense Webster, Diamond Bar, California, USA), using a 3D electroanatomic mapping system (CARTO, BiosenseWebster). A 6Fr diagnostic catheter placed in the right atrium served as a temporal reference. Radiofrequency current was applied outside the ostia of all pulmonary veins, using the ablation catheter with a 4-mm open loop irrigated tip. The following power and temperature settings were used: irrigation rate 20 ml/min, maximum temperature 50° C, and maximum radiofrequency energy 30W. At each point, the radiofrequency current was applied until a voltage of <0.1 mV was achieved, with a maximum of 60 s/point. The procedure was considered successful when pulmonary vein isolation was confirmed by the recording of entrance block during SR or pacing in the coronary sinus. All patients received heparin intravenously (activated clotting time >300 sec) to avoid thrombo-embolic complications during the catheter ablation procedure. After RFCA, the rhythm was continuously monitored until discharge.

Statistical analysis

Continuous data are presented as mean ± standard deviation. Categorical data are presented as absolute numbers or percentages. Independent-samples T test and Wilcoxon rank-test were used to compare continuous variables, as appropriate, and χ^2 test was used to compare

categorical variables. Sequential data measurements were analyzed by the general linear model (GLM) procedure for repeated measures. For all tests, a p value <0.05 was considered significant. A statistical software program SPSS 15.0 (SPSS Inc, Chicago, Il, USA) was used for statistical analysis.

RESULTS

Baseline clinical characteristics of the study population are summarized in Table 1. At baseline, RT3DE revealed a mild enlargement of LA volume and a moderate reduction in LA_{EF}, LA_{active} and $LA_{reservoir}$ (Table 2), as compared to the reference values for a normal LA (9,14). Left ventricular systolic and diastolic functions were normal and in 27 patients MR was present (mild n = 24; moderate n = 3) (Table 3). Six patients were in AF at the baseline evaluation and all had a recurrence of AF during follow-up. In these patients, LA_{preA}, LA_{active}, $LA_{passive}$ and LV diastolic function could therefore not be assessed.

Table 1. Baseline clinical characteristics of the total study population and of patients with and without recurrence of AF after radiofrequency catheter ablation

Variable	Total study population n = 57	Sinus rhythm group n = 38	Atrial fibrillation group n = 19
Age (years)	56 ± 9	57 ± 9	53 ± 9
Male/Female	44/13	28/10	16/3
Body surface area (m^2)	2.1 ± 0.2	2.1 ± 0.3	2.1 ± 0.1
Atrial fibrillation: Paroxysmal/Persistent	45 (79%) / 12 (21%)	34 (89%) / 4 (11%)	11 (58%) / 8 (42%)*
Duration atrial fibrillation (years)	4.6 ± 4.1	4.5 ± 4.1	4.6 ± 4.1
Number of anti-arrhythmic drugs per patient	3 ± 1	3 ± 1	3 ± 1
ACE-inhibitor and/or Angiotensin receptor blocker	26 (46%)	17 (45%)	9 (47%)
Heart rate (beats/minute)	62 ± 20	60 ± 13	66 ± 36
Hypertension	25 (44%)	13 (34%)	11 (58%)
Diabetes mellitus	6 (11%)	6 (15%)	0 (0%)
Coronary artery disease	3 (5%)	2 (5%)	1 (5%)

*p <0.05 SR group versus AF group.

After a mean follow-up of 7.9 ± 2.7 months, 38 patients (67%) had successful RFCA (SR group), whereas 19 patients (33%) had recurrence of AF (AF group). Of note, these patients were classified in the same group also at 3 months follow-up evaluation. No significant differences were found in the baseline clinical characteristics between the AF and SR groups, except for the percentage of patients with persistent AF (Table 1). At baseline, RT3DE showed larger LA_{max} in the AF group than in the SR group (31 ± 8 vs. 26 ± 8 mL/m^2, p <0.05), but no significant differences in LA and LV function (Table 2 and 3). Conventional 2D color-Doppler echocardiography revealed a comparable LV diastolic function and prevalence of MR (mild/ moderate) between

Table 2. Left atrium (LA) volumes and function at baseline, immediately after and 3 months after the ablation procedure in the total study population and in patients with or without recurrence of AF

Variable	Total study population n = 57	Sinus rhythm group n = 38	Atrial fibrillation group n = 19	p value
LA volumes				
LA maximum volume (mL/m²)				**<0.01§**
Baseline	28 ± 9	26 ± 8	31 ± 8	<0.05
After ablation		26 ± 8	31 ± 8	<0.05
3 months follow-up		23 ± 7*	32 ± 8	<0.001
LA minimum volume (mL/m²)				**<0.01§**
Baseline	14 ± 6	13 ± 5	16 ± 7	NS
After ablation		12 ± 5	17 ± 6	<0.01
3 months follow-up		10 ± 4*	18 ± 6	<0.001
LA volume preA (mL/m²)				**<0.01§**
Baseline	16 ± 5	16 ± 5	18 ± 6	NS
After ablation		16 ± 5	18 ± 4	NS
3 months follow-up		14 ± 5*	20 ± 6*	<0.01
LA function				
LA total emptying fraction (%)				**<0.01§**
Baseline	50 ± 11	52 ± 10	47 ± 13	NS
After ablation		52 ± 10	44 ± 12	<0.05
3 months follow-up		58 ± 10*	42 ± 11*	<0.001
LA passive emptying fraction (%)				**NS§**
Baseline	39 ± 9	39 ± 9	38 ± 10	NS
After ablation		39 ± 9	35 ± 10	NS
3 months follow-up		38 ± 9	35 ± 9	NS
LA active emptying fraction (%)				**<0.001§**
Baseline	22 ± 8	22 ± 8	24 ± 7	NS
After ablation		21 ± 6	17 ± 7	NS
3 months follow-up		33 ± 9*	15 ± 9*	<0.001
LA expansion index (%)				**<0.01§**
Baseline	110 ± 48	116 ± 45	101 ± 55	NS
After ablation		117 ± 43	92 ± 49	NS
3 months follow-up		152 ± 54*	78 ± 35*	<0.001

*p <0.01 (GLM for repeated measures within subjects); § p value derived from GLM for repeated measures between subjects (sinus rhythm vs. atrial fibrillation).

the 2 groups (Table 3). Immediately after the RFCA procedure, no significant changes in LA volumes were observed (Table 2). However, after 3 months of follow-up, a significant decrease in LA volumes was noted in the SR group, involving LA_{max}, LA_{min} and LA_{preA} volumes. Conversely, the AF group showed a trend towards an increase in LA volumes during follow-up (Table 2). An example of a patient in the SR group with a significant reduction of LA_{max} and LA_{min} is shown in Figure 2. In both groups, no significant changes in LA function were noted immediately after the RFCA procedure. However, after 3 months of follow-up, a significant improvement of LA_{active} and $LA_{reservoir}$ was noted in the SR group, whereas in the AF group these parameters showed a significant deterioration (Figure 3). In contrast, $LA_{passive}$ function did not change significantly in both groups. In concordance with the changes in LA_{active}, a significant improvement in LA_{EF} was observed in the SR group, while a significant deterioration in LA_{EF} was observed in the AF group (Table 2).

Table 3. Left ventricular function at baseline and 3 months after the ablation procedure in the total study population and in patients with or without recurrence of atrial fibrillation

Variable	Total study population n = 57	Sinus rhythm group n = 38	Atrial fibrillation group n = 19
Left ventricular ejection fraction (%)			
Baseline	57 ± 9	58 ± 9	57 ± 11
3 months follow-up		59 ± 10	57 ± 8
E/A			
Baseline	1.2 ± 0.6	1.1 ± 0.4	1.4 ± 0.6
3 months follow-up		1.2 ± 0.2	1.3 ± 0.7
Deceleration time (ms)			
Baseline	194 ± 53	196 ± 51	192 ± 48
3 months follow-up		199 ± 40	195 ± 42
Mitral regurgitation, n (absent/mild/moderate/severe)			
Baseline	30/24/3/0	21/16/1/0	9/8/2/0
3 months follow-up		25/13/0/0*	9/8/2/0

* p <0.01 baseline vs. follow-up.

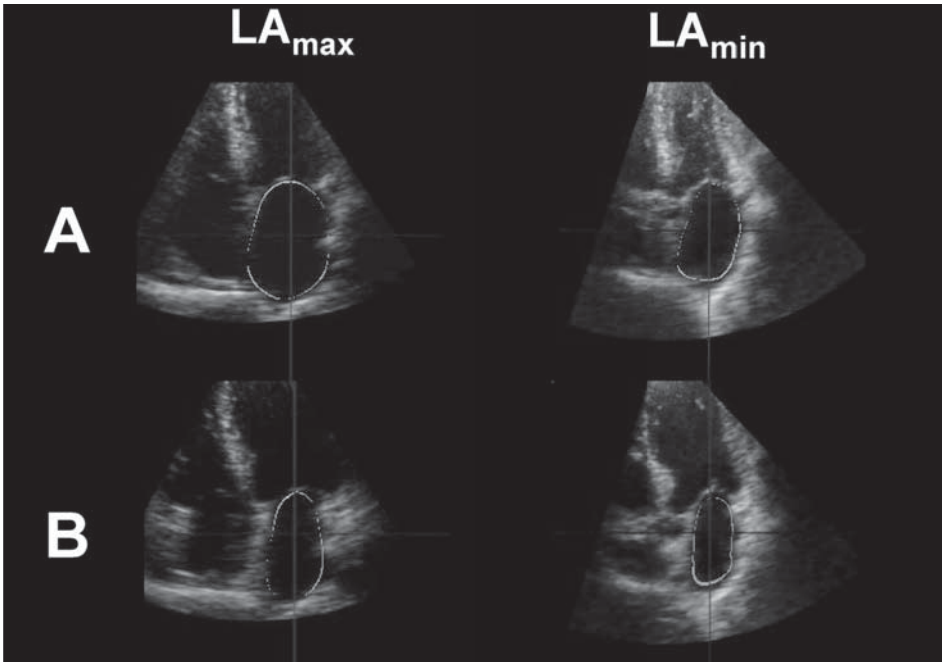

Figure 2. Example of a patient with significant reduction of LA_{max} and LA_{min}, 3 months after the RFCA (panel B vs. panel A). LA_{max} decreased from 83 to 66 mL/m^2 and LA_{min} decreased from 44 to 33mL/m^2.

Mean LV ejection fraction was 58 ± 9% in the SR group and 57 ± 11% in the AF group (p = NS) and no significant changes were observed during follow-up. Similarly, LV diastolic function was normal in both groups before the RFCA procedure and did not change during follow-up (Table 3). However, 12 patients in the SR group and 3 patients in the AF group had an abnormal

LV relaxation based on E/A <1. For these patients an improvement in LV filling pattern was noted in the SR group only (E/A ratio from 0.7 ± 0.2 to 1.6 ± 0.5, p <0.01). Only 3 patients had clinically relevant MR (moderate or severe) and a significant improvement in the degree of MR after RFCA was only observed in the SR group (Table 3).

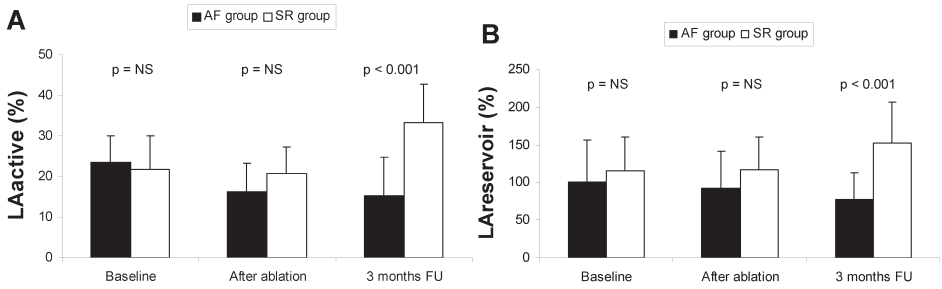

Figure 3. Left atrium active emptying fraction (LA_{active}; panel A) and expansion index ($LA_{reservoir}$; panel B) at baseline, immediately after catheter ablation and at 3 months follow-up (FU) in SR and AF groups.

DISCUSSION

The main findings of the current study can be summarized as follows: 1) three months after RFCA, a significant reduction in LA volumes and a clear improvement of LA active contraction and LA reservoir function was observed in patients with a successful RFCA procedure; 2) patients with recurrence of AF after RFCA showed a trend towards a worsening of LA volumes and function

Real-time 3-dimensional echocardiography

In the present study, RT3DE was used to assess LA volumes and function in patients treated with RFCA for AF. The assessment of LA size is fundamental in the management of patients with AF, since it has important prognostic value and is used as a surrogate marker of therapy success (15-18). The most recent recommendations for cardiac chamber quantification indicate LA volume as the preferred measurement of LA size (9). However, the majority of the previous studies only evaluated LA diameter and LA area, using conventional 2D echocardiography (16,18,19). Although most frequently used, 2D echocardiography is limited for the assessment of LA volume by significant geometric assumptions and low reproducibility due to diverging position and orientation of imaging planes. RT3DE has been demonstrated to be more accurate for LA volumes quantification, with the most favorable test-retest variation (1,2,4). In addition to LA volumes, assessment of LA function is of particular significance in patients treated with RFCA for AF. However, accurate non-invasive measurements for LA function are still lacking. Recently, initial studies have proposed tissue Doppler imaging (TDI) and 2D strain as new modalities to assess LA myocardial function (20,21). However, these techniques need to be further validated for this purpose and have some limitations related to the angle dependency of TDI (21) and the

difficult analysis of LA systole with 2D strain (20). In contrast, RT3DE is well validated (3,4,22) and provides a unique combination of an accurate measurement of LA volumes together with a rapid and automatic detection of phasic changes of LA volumes that provides detailed information of the different LA functions.

Effect of RFCA on LA volumes and function

The relationship between LA enlargement and AF is complex: structural changes of the LA may be related several factors including 1) pressure or volume overload due to underlying structural heart disease; 2) the increased LV filling pressure induced by the tachyarrhythmia; 3) AF itself (23,24). Supporting the latter hypothesis, abnormal atrial histology (fibrosis, necrosis and inflammation) has been found uniformly in patients with lone AF (25). Furthermore, LA dilatation has been directly correlated with the duration of AF, as a result of LA electrical and structural remodeling (18). In the present study, mild dilatation of the LA was noted at baseline using RT3DE. This may be explained by the relatively low prevalence of patients with persistent AF and with structural heart disease (Table 1). Of note, the AF group, compared to the SR group, demonstrated larger baseline LA volumes, probably related to the higher percentage of persistent AF. Furthermore, after 3 months a significant decrease in LA volumes was noted in patients with successful RFCA. These results are in agreement with previous studies that showed a significant reduction in LA volumes after conversion of AF to SR, either by electrical cardioversion or RFCA (6,14,26). The reduction in LA_{min} as observed in the present study is most probably the direct result of the improvement of LA active contraction; whereas the reduction in LA_{max} is reflecting a true reverse remodeling that is related with the long-lasting restoration of SR. Although LA reverse remodeling may also be ascribed to atrial scarring caused by RFCA, this is very unlikely since LA volumes tended to worsen in patients with recurrence of AF during follow-up.

In addition, an improvement in LA function was observed in patients who maintained SR after RFCA. The LA serves multiple functions. During LV systole and isovolumic relaxation, it operates as a "reservoir" that receives blood from pulmonary veins and stores energy in the form of pressure; during the early diastole, it operates as a "conduit" for transfer blood into the LV after mitral valve opening; during the late diastole the "active" contraction of LA contributes to LV stroke volume by 20-30% (22,23). To interpret the baseline and follow-up findings of the present study, it is important to consider that the major determinants of LA_{active} are the heart rhythm, the atrial contractility and the LA_{preA} (Frank-Starling effect) (3,11). The $LA_{reservoir}$ is rather influenced by LV systolic function (mitral annulus displacement) and by LA wall stiffness (11,27). On the contrary, $LA_{passive}$ is mainly related to LV diastolic function (11,28).

In the present study, a moderate reduction of LA_{active} and $LA_{reservoir}$ was noted at baseline evaluation. Conversely, no significant impairment of $LA_{passive}$ was observed. Since LV systolic and diastolic functions were normal on average and LA_{preA} was even decreased compared to

the normal values, the reduction in LA_{active} and $LA_{reservoir}$ is most probably related to the effect of AF itself on the contractility and the stiffness of atrial walls.

Immediately after RFCA, no significant changes in LA functions were found, but LA_{active} tended to worsen. This finding occurred in both the SR and AF groups and can be related to the phenomenon of atrial "stunning" (29). After 3 months of follow-up, a significant improvement in LA_{active} and $LA_{reservoir}$ was noted in the SR group, whereas in the AF group these parameters showed a significant deterioration. Since LV systolic and diastolic functions did not change after RFCA and LA_{preA} was even decreased, the functional improvement in the SR group is most probably related to a favorable effect of the long-lasting restoration of SR on the intrinsic characteristics of the atrial myocardium (24). These findings are in line with previous studies (6,14) and carry important clinical implications, since they may translate into a reduced risk of AF recurrences and thrombo-embolic complications at long-term follow-up (24). However, the exact impact of LA reverse remodeling and improvement of LA function on cardiovascular outcomes remains to be determined.

The results of the present study need to be confirmed in a larger population with longer clinical and echocardiographic follow-up. In addition, in patients with paroxysmal AF, asymptomatic recurrences cannot be excluded and may have influenced the success rate in the present study.

CONCLUSIONS

In conclusion, the effect of RFCA on LA size and function can be accurately evaluated with RT3DE. In the present study, a significant reverse remodeling and functional improvement of the LA was noted in patients who maintain sinus rhythm after RFCA. In contrast, a deterioration of LA volumes and function was observed in patients with recurrence of AF.

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