Left Atrial Function After Radiofrequency Catheter Ablation of Atrial Fibrillation

– Can Pre-Ablation Function Predict Contractile Improvement During Follow-up? –

Marina Antolini, MD; Alessandro Brustio, MD; Mara Morello, MD; Federica Bongiovanni, MD; Cristina Fornengo, MD; Cristina Gallo, MD; Simone Frea, MD; Walter Grosso Marra, MD, PhD; Federico Ferraris, MD; Laura Bergamasco, PhD; Fiorenzo Gaita, MD

Background: Data are lacking on the effect of radiofrequency catheter ablation (RFCA) on atrial function. The aim of this study was to determine a cut-off of pre-ablation left atrial (LA) function in order to predict atrial functional recovery after RFCA.

Methods and Results: A total of 64 atrial fibrillation (AF) patients who underwent RFCA were enrolled (age, 59.05 ± 12.09 years; 36% persistent AF; LA volume 37.8 ± 13.6 ml/m²). LA emptying fraction (LAEF), LA active fraction (LAAEF), LA passive emptying fraction (LAPEF) and LA expansion index (LAEI) were evaluated in sinus rhythm before and 48 h, 15 days, 1, 2, 3 and 9 months after ablation. LA function improvement was defined as any positive increase in LAEF compared with baseline. On univariate and multivariate analysis only baseline atrial function proved to be an independent predictor of LA function improvement after ablation ($P=0.002$; OR=0.001; 95% CI: 0.000–0.099). On receiver operating characteristic analysis (AUC=0.70), cut-off for baseline LAEF was 40%. At 9 months, patients with LAEF <40% had significant improvement in atrial performance (LAEF, $P=0.01$; LAAEF, $P=0.036$; LAEI, $P=0.004$); a significant negative correlation between baseline LAEF and LA function improvement was observed ($r=-0.62$; 95% CI: -0.83 to -0.26 ; $P_{(r=0)} < 0.002$).

Conclusions: Baseline LAEF is an independent predictor of LA function recovery after RFCA. The beneficial effect of AF ablation is most evident in patients with LAEF <40%. (*Circ J* 2015; **79**: 2576–2583)

Key Words: Ablation; Atrial fibrillation; Echocardiography

Radiofrequency catheter ablation (RFCA) is an effective treatment in rhythm-control therapy for atrial fibrillation (AF), with a reduction in AF recurrence ranging from 50 to 80%.^{1–3} By promoting a reduction in arrhythmic burden, RFCA improves symptoms and quality of life.^{4,5}

Despite both structural and functional changes after RFCA having been extensively studied, the effect of AF ablation on left atrial (LA) function has not yet been sufficiently determined and remains a pivotal topic also with regard to the consequences of decision on whether to discontinue anticoagulation after successful ablation.⁶ In patients with impaired LA function, the risk of thrombus formation is potentially augmented, irrespective of the classical risk factors.⁷

Pre-ablation LA function has been identified as an indepen-

dent predictor of LA function improvement at follow-up, but previous studies have not identified a cut-off of LA function able to predict LA functional recovery.⁸

The aim of this mono-center prospective study was therefore to clarify the effect of AF ablation on LA function according to baseline atrial performance.

Methods

Patient Enrollment

From March to December 2013, all consecutive patients who underwent catheter ablation for paroxysmal or persistent AF in the electrophysiology laboratory were considered for enrollment. Only those who presented in sinus rhythm at baseline

Received February 17, 2015; revised manuscript received August 17, 2015; accepted September 4, 2015; released online October 8, 2015
Time for primary review: 14 days

Division of Cardiology, Cardiovascular and Thoracic Department, “Città della Salute e della Scienza” Hospital and Department of Medical Sciences, University of Turin, Turin, Italy

Mailing address: Marina Antolini, MD, Division of Cardiology, Cardiovascular and Thoracic Department, “Città della Salute e della Scienza” Hospital and Department of Medical Sciences, University of Turin, C.so A.M. Dogliotti, 14, 10126, Turin, Italy. E-mail: marina.antolini@gmail.com

ISSN-1346-9843 doi:10.1253/circj.CJ-15-0184

All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

were included in the study. The exclusion criteria were: significant heart valve disease (more than moderate), unstable coronary artery disease, severe left ventricular (LV) hypertrophy, poor LV systolic function (LV ejection fraction [LVEF] <50%), decompensated pulmonary or thyroid disease, and severe procedural complications. Written informed consent for catheter ablation and transesophageal echocardiography was required. The study was approved by the institutional review board.

Electrophysiological Study and Catheter Ablation

As described in our previous report,⁹ patients were routinely admitted to the hospital 1–2 days before ablation. Oral anticoagulants were administered for at least 1 month before the procedure (international normalized ratio [INR] target between 2 and 3) and continued during the perioperative period. All anti-arrhythmic drugs were stopped for 5 half-lives before the procedure. A decapolar electrode catheter was positioned in the coronary sinus for pacing and recording. The LA was accessed via patent foramen ovale, when present, or via transseptal puncture (through 8-F long sheath; Fast-Cath or SL0, St. Jude Medical, St. Paul, MN, USA), continuously perfused with heparinized solution. A multipolar catheter (Lasso, Biosense Webster, Diamond Bar, CA, USA; or Inquiry Optima, St. Jude Medical; or Orbiter, Bard, Lowell, MA, USA) was inserted through the long sheath to map the pulmonary veins ostia. An irrigated-tip ablation catheter (Navistar or Thermocool, Biosense Webster or Coolpath, St. Jude Medical) was advanced into the LA through the same hole whenever possible; otherwise, a second transseptal puncture was performed. After transseptal puncture, i.v. unfractionated heparin was administered as a bolus (80 U/kg), and additional boluses were given throughout the procedure to maintain an activated clotting time (ACT) >250 s. After positioning of the catheters in the LA, the venous sheath was moved into the right atrium. ACT was determined 30 min after the transseptal puncture and subsequently every 30 min. A 3-D reconstruction of the LA and pulmonary veins ostia, with the use of an electroanatomic mapping system (Carto, Biosense Webster, or Nav-X, St. Jude Medical), was performed in all patients. For paroxysmal AF, the endpoint of the ablation procedure was to obtain complete electric pulmonary veins isolation. For persistent forms pulmonary veins isolation was accompanied by the creation of extralinear lesions connecting the upper pulmonary veins ostia (roof line), and the left inferior pulmonary vein down to the mitral annulus (left isthmus); when necessary, a line connecting the right inferior pulmonary vein to the mitral annulus (right isthmus) and ablation of fragmented atrial electrograms were performed to complete elimination of the potentials. RF was applied with power output up to 30 W close to the pulmonary vein ostia and up to 40 W while creating the roof line and the left mitral isthmus line, with an irrigation rate of 15–35 ml/min (0.9% saline infused with the Cool Flow Pump, Biosense Webster) to maintain a tip temperature <45°C.

Echocardiography

Before ablation, extensive transthoracic and transesophageal echocardiography evaluation was performed on all patients in order to exclude the presence of thrombi in LA appendage and to evaluate global cardiac dimension and function. Follow-up studies were scheduled at 48 h, 2 weeks, 1, 2, 3 and 9 months. All echocardiographic assessments were performed using a Philips iE33 (Philips Medical Systems, Andover, MA, USA) system with a 2.5-MHz transducer, by 2 operators who were blinded to prior results and to one another's results. All measurements were acquired from 3 consecutive beats during sinus

rhythm. All data were collected according to current guidelines.^{10,11} LA volume was obtained from apical 2- and 4-chamber views and was indexed to body surface area; maximum (LV end-systole, just before mitral valve opening) minimum (LV end-diastole at the start of QRS) and pre-systolic volume (at peak of P wave of simultaneously recorded electrocardiogram [ECG]) were obtained using Simpson's rule, taking care to exclude pulmonary veins and the LA appendage. We are aware that the evaluation of LA function on echocardiography is not standardized, given that different methods have been used to assess LA function in research and in clinical practice;^{12,13} the comparison of data taken at different times before and after ablation should, however, compensate for biases intrinsic to a specific approach. The LA serves multiple functions: reservoir during LV systole; conduit for blood transiting during early diastole and active contractile pump in late diastole.¹⁴ Phasic volumes were used to calculate LA emptying fraction (LAEF) ($[\text{maximum} - \text{minimum LAV}] / \text{maximum LAV} \times 100$), LA active emptying fraction (LAAEF) ($[\text{pre-systolic} - \text{minimum LAV}] / \text{pre-systolic LAV} \times 100$), LA passive emptying fraction (LAPEF) ($[\text{maximum} - \text{pre-systolic LAV}] / \text{maximum LAV} \times 100$) and LA expansion index (LAEI) ($[\text{maximum} - \text{minimum LAV}] / \text{minimum LAV} \times 100$). More recent methods of evaluating LA function, such as color-coded tissue-Doppler based strain and strain rate and 2-D speckle-tracking based strain and strain rate were not available during the study period.

Follow-up

Patients were discharged 1 or 2 days after the procedure and were seen at hospital at 3-month intervals after ablation. A clinical cardiologist decided on anticoagulant therapy management according to patient risk profile and history; patients with easily inducible residual AF were prescribed anti-arrhythmic drugs. Arrhythmic events were assessed on symptoms, 12-lead ECG, 24-h Holter and implantable loop recorder recordings. AF recurrence was defined as the detection of AF and/or atrial tachycardia ≥ 3 months after ablation. Recurrent events were treated with anti-arrhythmic drugs and/or electrical cardioversion as soon as possible. During follow-up no further RFCA were required to treat AF recurrences.

Statistical Analysis

Data were analyzed using SPSS (version 12.0; Chicago, IL, USA). Continuous variables are expressed as mean $\pm$ SD and categorical variables as count and percentage. The discriminating ability of the basal atrial function for the prediction of variation of LA function at mid-term follow-up was assessed using receiver operating characteristic (ROC) curves: the cut-off was obtained by maximizing the harmonic mean of sensitivity (SN) and specificity (SP) of the various levels. In order to evaluate atrial function at different time points, Friedman's non-parametric test and Wilcoxon's non-parametric test were applied. According to normality testing, strength and direction of the correlation was evaluated with Pearson or Spearman rho test for all patients.

The lack of inter- and intra-operator variability was assessed using Wilcoxon's non-parametric test for matched data, Pearson's linear coefficient r , intraclass correlation coefficient (ICC), etasquare and Bland-Altman plot. The standard deviation s of the differences $(x_2 - x_1)$ between the 2 measurements used to draw the limits of agreement on Bland-Altman plot and the mean m of the abscissas $(x_2 + x_1) / 2$ were used also to compute the coefficient of repeatability (CR) = 1.96 s and the coefficient of variation (CV) = 100 s / m .

Univariate and multivariate logistic regression analysis were

Table 1. Clinical and Echocardiographic Data vs. LAEF

	Total (n=64)	Group 1 (LAEF <0.40) (n=31)	Group 2 (LAEF ≥0.40) (n=33)	P-value
Clinical data				
Age (years)	59.05±12.09	59.97±8.32	58.18±14.87	0.747
Sex (male)	48 (75)	26 (83)	22 (66)	0.746
Hypertension	45 (70)	22 (69)	23 (72)	0.911
Diabetes	6 (9)	4 (12)	2 (6)	0.348
CAD	8 (12)	4 (12)	4 (12)	0.658
Persistent AF	23 (36)	14 (44)	9 (28)	0.136
AF duration (months)	71.00±84.18	82.77±97.20	59.94±69.51	0.460
Previous AF ablation	10 (16)	7 (22)	3 (9)	0.137
Amiodarone	15 (23)	8 (26)	7 (21)	0.241
Sotalol	10 (16)	3 (10)	7 (21)	0.160
IC anti-arrhythmic drugs	35 (55)	14 (45)	21 (63)	0.184
AF recurrence	14 (22)	7 (22)	7 (22)	0.895
RFCA ablation energy (W)	1,117.71±608.63	1,275.32±730.65	981.59±454.00	0.060
Echocardiographic data				
End-diastolic LV diameter (mm)	48.65±6.11	49.00±6.62	48.31±5.65	0.695
LV ejection fraction (%)	60.02±6.36	59.42±8.03	60.59±4.23	0.943
E/A	1.24±0.56	1.38±0.6	1.13±0.51	0.544
E/e'	8.64±3.04	8.96±3.00	8.37±3.11	0.797
LA diameter (mm)	42.6±8.6	44.55±8.77	40.94±8.25	0.075
LA area (cm ²)	24.3±7.4	24.78±4.97	23.87±9.15	0.094
LA maximum volume (ml/m ²)	37.8±13.6	40.19±12.72	37.63±14.33	0.052
LA minimum volume (ml/m ²)	23.2±10.7	28.39±10.67	18.92±8.68	0.0001
LA pre-systolic volume (ml/m ²)	29.3±11.9	32.56±11.98	26.68±11.36	0.004
LA emptying fraction	0.42±0.13	0.31±0.06	0.51±0.08	0.0001
LA active emptying fraction	0.22±0.13	0.13±0.08	0.29±0.12	0.0001
LA passive emptying fraction	0.25±0.12	0.19±0.09	0.30±0.13	0.001
LA expansion index	0.80±0.46	0.45±0.13	1.11±0.43	0.0001

Data given as mean±SD or n (%). AF, atrial fibrillation; CAD, coronary artery disease; IC, IC anti-arrhythmic drugs; LA, left atrial/atrium; LAEF, LA emptying fraction; LV, left ventricular; RFCA, radiofrequency catheter ablation.

used to identify clinical factors associated with LA function improvement after RFCA. LA function improvement was defined as any positive increase in LAEF compared with baseline. Variables with $P \leq 0.10$ in the univariate models were included in the multivariate logistic regression. The results of the two analyses were coherent on overlapping issues. Significance was set at $P < 0.05$.

Results

Inter-Operator Reliability Analysis

The inter-operator reliability was satisfactory, obtaining good agreement between the various independent statistical approaches (Wilcoxon's $P=0.72$; Pearson's $r=0.72$; ICC=0.850; $\eta^2=0.921 \pm 0.079$; CR=33.1; CV=20%).

Baseline Characteristics and Follow-up

Among patients referred for ablation of paroxysmal/persistent AF, 37 did not meet inclusion criteria (AF or atrial tachycardia at baseline evaluation, 43%; history of significant structural heart disease, 11%; inability to complete follow-up, 41%).

Baseline clinical and echocardiographic characteristics of the enrolled patients ($n=64$) are listed in **Table 1**. The average age was 59.05 ± 12.09 years, 48 (75%) were male, and 45 (70%) had concomitant hypertension. All patients had New York Heart Association (NYHA) class I. Mean LVEF was

60.71 ± 4.76 ; 67% patients had mild mitral regurgitation. NYHA class, LVEF and the degree of mitral regurgitation did not significantly change during follow-up (all patients maintained NYHA class I at the end of follow-up; mild mitral regurgitation: baseline 67% vs. end of follow-up 69%, $P=0.97$; EF: baseline $60.71 \pm 4.76\%$ vs. end of follow-up $61.48 \pm 3.27\%$, $P=0.251$). Twenty-three patients (36%) had persistent AF. Mean arrhythmia duration since diagnosis was 71.00 ± 84.18 months. Mean indexed LA volume was 37.8 ± 13.6 ml/m² and LAEF was 0.42 ± 0.13 . Successful pulmonary vein isolation was completed in all patients; linear lesions were created in 1 patient while ablation of fragmented atrial electrograms was carried out in 2 patients. During a 9-month follow-up, AF or atrial tachycardia recurred in 14 patients (22%).

Identification of LAEF Cut-Off

On univariate analysis only baseline LAEF was a predictor of LAEF improvement ($P=0.002$, OR=0.001, 95% CI: 0.000–0.099). Age, gender, hypertension, persistent AF, previous AF ablation, AF duration, AF recurrence after ablation, LA volume, E/e' ratio and RFCA ablation energy power did not reach statistical significance. On multivariate analysis LAEF was confirmed as an independent predictor of LAEF improvement ($P=0.007$, OR=0.000, 95% CI: 0.000–0.007).

On ROC curve analysis, the discriminating ability of LAEF was fair (area under the curve=0.70; 95% CI: 0.54–0.86). On

Table 2. LA Function Data								
	Baseline	48 h	15 days	1 month	2 months	3 months	9 months	P-value
Overall population								
LAEF	0.42±0.13	0.39±0.12	0.39±0.14	0.41±0.14	0.39±0.13	0.43±0.14	0.42±0.15	0.384
LAAEF	0.22±0.13	0.21±0.10	0.20±0.14	0.20±0.15	0.19±0.15	0.25±0.14	0.23±0.14	0.387
LAPEF	0.25±0.12	0.24±0.16	0.25±0.12	0.26±0.12	0.24±0.13	0.25±0.14	0.26±0.14	0.936
LAEI	0.80±0.46	0.70±0.34	0.72±0.42	0.82±0.58	0.73±0.42	0.87±0.53	0.88±0.67	0.247
Group 1 (LAEF <0.40)								
LAEF	0.31±0.06	0.37±0.12	0.35±0.13	0.36±0.14	0.37±0.11	0.43±0.17	0.42±0.16	0.01
LAAEF	0.13±0.08	0.20±0.09	0.17±0.14	0.15±0.13	0.12±0.14	0.22±0.14	0.24±0.16	0.036
LAPEF	0.19±0.09	0.23±0.19	0.31±0.26	0.30±0.22	0.29±0.20	0.34±0.23	0.28±0.13	0.061
LAEI	0.45±0.13	0.65±0.36	0.60±0.32	0.63±0.35	0.62±0.29	0.91±0.62	0.90±0.85	0.004
Group 2 (LAEF ≥0.40)								
LAEF	0.51±0.08	0.41±0.10	0.42±0.14	0.45±0.13	0.41±0.15	0.42±0.12	0.44±0.12	0.058
LAAEF	0.29±0.12	0.21±0.11	0.23±0.13	0.25±0.14	0.25±0.14	0.27±0.14	0.23±0.12	0.375
LAPEF	0.30±0.13	0.25±0.12	0.25±0.12	0.27±0.13	0.22±0.12	0.23±0.18	0.26±0.14	0.097
LAEI	1.11±0.43	0.76±0.32	0.83±0.47	0.97±0.69	0.82±0.49	0.83±0.44	0.86±0.39	0.17

Data given as mean±SD. LAAEF, LA active emptying fraction; LAEI, LA expansion index; LAPEF, LA passive emptying fraction. Other abbreviations as in Table 1.

maximization of the harmonic mean of SN and SP and agreement with Cohen's coefficient, a cut-off of 40% was identified (SN, 65%; SP, 63.6%; $k=0.29$; Figure 1).

The subjects were then divided accordingly into 2 groups: group 1, baseline LAEF<40%; and group 2, LAEF ≥40%. There were no significant differences in clinical characteristics such as age, sex, AF type and duration between the 2 groups. Persistent AF was more frequent in group 1 and AF duration was shorter in group 2. No significant differences were noted in pharmacotherapy at baseline between the 2 groups. During follow-up, 2 patients in group 1 changed therapy, while in group 2 only in 1 patient had pharmacotherapy modified after RFCA ($P=0.265$). Patients with LAEF below the cut-off were more likely to have larger atria (LA maximum volume 82.42 ± 24.92 vs. 71.51 ± 31.51 ml, $P=0.052$; LA minimum vol-

ume 57.14 ± 21.28 vs. 35.70 ± 18.06 ml, $P=0.0001$; LA pre-systolic volume 66.00 ± 23.55 vs. 50.06 ± 23.81 ml, $P=0.004$; Table 1).

LA Function After Ablation

In the overall population LAEF did not differ significantly at 9-month follow-up compared with baseline ($P=0.384$). Similar results were obtained for LAPEF and LAEI.

On comparison of the 2 LAEF subgroups, an opposite trend was seen. In group 1 a significant improvement of LAEF, LAAEF and LAEI was recorded, accompanied by an increase in LAPEF, even if it did not reach statistical significance. In group 2 a global reduction in LAEF was instead seen (Table 2).

In group 1 LAEF showed an early improvement within 48 h, with a subsequent slight reduction until 1 month, followed by continuous improvement up to the end of the 9-month follow-

up. A similar trend was seen for LAPEF. LAPEF however, had minimal reduction between the first and the second month, with good improvement at 3 months of follow-up. Only LAEF showed constant improvement during the entire follow-up.

In group 2 each function parameter showed a reduction within the second month, with a following improvement until the end of follow-up, without, however, reaching the baseline values (Figure 2).

Regarding LA dimensions, in group 1 all phasic volumes (maximum, minimum and pre-systolic) showed a reduction at the end of follow-up (maximum volume, 40.19 ± 12.72 ml/m² vs. 39.47 ± 12.36 ml/m², $P=0.667$; minimum volume, 28.39 ± 10.67 ml/m² vs. 25.74 ± 11.88 ml/m², $P=0.059$; pre-systolic volume, 32.56 ± 11.98 ml/m² vs. 27.47 ± 9.14 ml/m², $P=0.028$). In group 2 maximum and pre-systolic volume appeared to be reduced at the end of follow-up (maximum volume, 37.63 ± 14.33 ml/m² vs. 34.28 ± 11.51 ml/m², $P=0.346$; pre-systolic volume, 26.68 ± 11.36 ml/m² vs. 24.02 ± 7.79 ml/m², $P=0.135$), while minimum dimensions showed an increase (minimum volume, 18.92 ± 8.68 ml/m² vs. 20.36 ± 10.85 ml/m², $P=0.935$).

Baseline LAEF and LAEF Variation After Ablation

Analysis of the correlation between baseline LAEF and its variation during follow-up showed a different trend for the 2 groups (Figure 3). In group 1 a significant negative correlation between baseline LAEF and its change after ablation was

observed ($r=-0.62$; 95% CI: -0.83 to -0.26 , $P_{(r=0)}<0.002$). For every 1% in baseline LAEF, there was an average 8% improvement in LAEF. No linear correlation was seen for patients with baseline LAEF $\geq 40\%$ (group 2).

Recurrence and LAEF After Ablation

Analyzing the overall population based on AF recurrence, no differences were seen in baseline LAEF between patients with or without AF recurrence (0.41 ± 0.15 vs. 0.41 ± 0.12 , $P=0.21$). LAEF remained almost unchanged during follow-up in both groups (AF recurrence: 0.41 ± 0.15 vs. 0.41 ± 0.17 , $P=0.779$; no AF recurrence: 0.41 ± 0.12 vs. 0.43 ± 0.14 , $P=0.992$).

Also, AF recurrence was not associated with LAEF improvement on univariate analysis ($P=0.683$, OR=0.818, 95% CI: 0.312–2.145).

Hemodynamic Status and LAEF After Ablation

Given that heart rate significantly increased after AF ablation (61.5 ± 13.2 vs. 66.7 ± 19.3 , $P=0.001$), this might have influenced LA volume and function. The change in heart rate, however, did not correlate with changes in maximum volume ($r=0.23$, 95% CI: -0.08 to $+0.49$, $P_{(r=0)}=0.14$) or LAEF ($r=0.24$, 95% CI: -0.07 to $+0.5$, $P_{(r=0)}=0.13$).

Hemodynamic status may have affected LA performance. No significant differences between the 2 groups in terms of loading conditions before ablation (E/e' ratio before ablation

$P=0.797$) and during follow-up (E/e' ratio variation $P=0.697$) were found. Nor did the change in loading conditions (represented by E/e' ratio) correlate with change in LAEF ($r=0.26$, 95% CI: -0.454 to $+0.385$, $P_{(r=0)}=0.970$).

Discussion

Change in LAEF According to Baseline LAEF

To the best of our knowledge this is the first study to determine a cut-off of pre-ablation LAEF able to predict recovery of function at mid-term follow-up. With regard to this, the key finding of the present study is the identification of a subgroup of patients with advanced LA remodeling (larger baseline volume and impaired baseline function) for whom it was possible to define a negative linear correlation between LAEF and LAEF improvement after ablation. The worse the pre-ablation function, the better the function improvement at mid-term follow-up. This evidence confirms similar data from Masuda et al, who noted a negative linear correlation between baseline LA function and subsequent function recovery after RFCA, without, however, defining a cut-off value of baseline function.⁸

Previous Studies on Changes in LA Function After RFCA

Data available about LA function recovery after ablation are still controversial,^{6,15–17} probably due to the different imaging techniques used (echocardiography, magnetic resonance angiography, or computed tomography), different parameters in LA function assessment and LA function evaluation at different timelines; finally, in the majority of these studies, LA measurements did not take into account whether patients were in AF or not at the time of image acquisition.

Among the many parameters available to assess LA performance, we chose LAEF. As defined here, LAEF is calculated as a ratio between LA volumes during different phases of cardiac cycle. Despite several studies showing that atrial volume measurements with different imaging techniques are not superimposable, the use of a ratio of the same volume at different cardiac phases, measured by the same operator, can help physicians to overcome this mismatch and make LAEF an optimal marker of atrial function.¹⁸ Moreover, the use of atrial phasic volumes not only allows an evaluation of global atrial function but also a complete assessment of different subtypes of function (active, passive, reservoir functions). The present results indicate that for patients with LAEF $<40\%$, LAPEF and EI appear to make the larger contribution to global LA function improvement, with LAAEF seeming to predominate during the first 3 months.

The majority of studies available evaluate LA function only at the end of the follow-up period, and a close analysis of how atrial performance changes during time is still lacking.^{19,20} In a small population study, Rodrigues et al noted an early reduction in atrial function within the first 12h after ablation, with a subsequent improvement at 6 months.¹⁹ The close monitoring of atrial function in the present study showed an unstable trend of atrial function during the follow-up period. It is well known that changes in LA function after RFCA depend on the balance between the beneficial effect of atrial remodeling and the harmful effect of edema and fibrosis. The predominant effect of 1 or more of these elements could explain the fluctuations observed in LA function. The pro-inflammatory effect of RFCA has been demonstrated in several studies, and the slight reduction of LAEF and LAAEF observed in the first month of the follow-up could be in part due to edema development.²¹ The improvement of LA performance between the first and the second month supports the hypothesis of the involve-

Figure 3. Changes in left atrial emptying fraction (LAEF) after ablation according to baseline LAEF. Significant negative correlation between baseline LAEF and the change in LAEF after ablation was seen.

ment of a reversible process. The effect of scar on atrial performance is still unclear. As demonstrated in a previous study, extensive LA scarring due to ablation results in impairment of LA function evaluated on magnetic resonance imaging (MRI).²² The exact beginning of this effect is not defined. Based on the present data, the effect of atrial scar appeared more evident between the third and the ninth month of follow-up. Furthermore, we can speculate that the effect of reverse remodeling, edema and fibrosis is different for the 2 subgroups LAEF $<40\%$ and LAEF $\geq 40\%$. Group 1 included patients with a larger baseline volume and a reduced baseline LAEF and had a slightly higher prevalence of persistent AF. Therefore, the improvement of atrial performance noted in those patients could reflect a predominance of reverse remodeling on RFCA fibrosis. Conversely, the initial slight reduction of LAEF seen in group 2 could be related to pro-inflammatory effects and edema development early after ablation, even assuming a smaller LA remodeling before RFCA.

Finally, in previous studies, measures of LA volumes and function were collected both during AF and sinus rhythm. In the present study, the occurrence of AF during echocardiography was an exclusion criterion: if one of the LA images was acquired during AF and the other in sinus rhythm, variation of minimum LA volume, in particular, may be underestimated.

Several studies reported a different trend in atrial function in patients with and without AF recurrence.^{23–25} In the present study atrial function recovery did not seem to be affected by the procedure efficacy (of eliminating the arrhythmia), possibly because of the lower rate of recurrence and the reduction of arrhythmic burden even in patients with AF recurrence.

Clinical Implications

The reduction of LA size and the increase in LA contractility seen in group 1 could act as prognostic factors of subsequent cardiovascular events. LA volume has been established as a prognostic marker for both adverse cardiovascular events as well as overall outcome.²⁶ To the best of our knowledge, the effective prognostic role of LA function improvement on cardiovascular events is still unknown. Data on surgical ablation showed how the absence of LA contraction on consecutive postoperative echocardiograms is associated with an increased risk of subsequent cerebral thromboembolic events.²⁷

The impact of AF ablation on thromboembolic risk is not clear and current opinion suggests that the decision on the long-term strategy of OAC should be based on baseline clinical risk scores, such as CHADS₂ and CHA₂DS₂-VASc.^{28–30} We can only suppose that patients with impaired baseline LAEF have a thromboembolic risk higher than that estimated only with traditional risk factors: despite sinus rhythm, high LA volumes and decreased LAEF may cause stasis of blood within the LA and LA appendage, promoting thrombus formation. After ablation, these patients had an important increase in LAEF, which could decrease blood stasis and presumably reduce thromboembolic risk during follow-up. At present, the level of LA function adequate to allow safe discontinuation of anticoagulation in this group of patients is still unknown. The finding of an evident improvement of LAEF in patients with depressed baseline function underlines the need for further studies to determine the net additional effect of LA function over the classical thromboembolic risk factors. Moreover, it must be noted how, despite that improvement in LA function, in both groups LAAEF, LAPEF and LAEI were considerably lower than in age-matched controls.³¹

In current clinical practice there are no predefined cut-offs of LA dimension and function able to guide physicians in selection of patients for RFCA. Previous studies have suggested that LA enlargement is a powerful predictor of AF ablation failure.³² The evidence of an LAEF improvement after RFCA, even in patients with moderate-severe LA enlargement, may encourage physicians to consider ablation even in this subgroup of patients.

Study Limitations

The present small sample size, and the large number of echocardiographic controls required for each patient, may have limited the power to detect predictors of function improvement on univariate analysis. Pre-ablation function, however, showed a high significance, demonstrating its strong association with LAEF during follow-up.

Considering sinus rhythm as a mandatory item in enrolment, patients with persistent AF who presented in sinus rhythm had an early persistent AF pattern. Certainly the less pronounced disease burden and substrate remodeling in this population might have influenced LA function recovery.

The 9-month follow-up limits the present results and conclusions only to the mid-term period, but progressive improvement of LA performance in patients with reduced baseline LAEF was seen, suggesting a good trend even on long-term follow-up. Of course this will require confirmation by studies covering a much longer follow-up period.

The monitoring of patients after ablation was carried out using ECG, 24-h Holter monitoring, implantable loop recorder and ambulatory visits. This method might underestimate the identification of recurrences, given that some asymptomatic recurrences might have been missed, preventing the identification of difference in LAEF change after ablation between the recurrence vs. non-recurrence group, as some other authors previously found.

Also, differences between fibrosis-preventing drugs (angiotensin-converting enzyme inhibitor and angiotensin receptor blockers) and anti-arrhythmic drugs were not evaluated, preventing elucidation of the net effect of ablation on LA recovery.

Furthermore, even if several studies have used 3-D echocardiography and strain/strain rate techniques, at the moment of enrollment they were not available in the present laboratory.³³

Moreover, despite its well known advantages, 2-D echocardiography has some limitations in assessing LA volume, mainly

due to difficulty in endocardial border tracing and the fact that it relies on geometrical assumptions that ignore LA geometry differences between individuals. Also, MRI is now considered to be the gold standard for LA dimension and function assessment, and LA volumes have been shown to be systematically underestimated on 2-D echocardiography compared with MRI, and LAEF are similar to those calculated using MRI.^{34,35}

Finally, different authors included LAA evaluation in LA function analysis. Even if complete LAA assessment remains mandatory before RFCA in order to avoid atrial thrombosis, it requires an invasive approach associated with well-known, even if rare, complications (laryngospasm, arrhythmias including cardiac arrest, esophageal perforation, hemorrhage from esophageal tumor and death).³⁶ The present study provided close monitoring of LA function (7 controls during 9-month follow-up) and transesophageal echocardiography for all the controls was not possible. Moreover we chose a simple index of LA function, easy to use even in ambulatory controls.

Acknowledgments

Conflict of Interest: None declared.

References

1. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation: Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012; **33**: 2719–2747.
2. Blandino A, Toso E, Anselmino M, Scaglione M, Gaita F. Radiofrequency catheter ablation of atrial fibrillation: How it has changed since 1996. *G Ital Cardiol* 2012; **13**(10 Suppl 2): 21S–28S.
3. JCS Joint Working Group. Guidelines for non-pharmacotherapy of cardiac arrhythmias (JCS 2011): Digest version. *Circ J* 2013; **77**: 249–274.
4. Reynolds MR, Walczak J, White SA, Cohen DJ, Wilber DJ. Improvements in symptoms and quality of life in patients with paroxysmal atrial fibrillation treated with radiofrequency catheter ablation versus antiarrhythmic drugs. *Circ Cardiovasc Qual Outcomes* 2010; **3**: 615–623.
5. Ejima K, Kato K, Arai K, Fukushima K, Fukushima N, Suzuki T, et al. Impact of atrial remodeling on the outcome of radiofrequency catheter ablation of paroxysmal atrial fibrillation. *Circ J* 2014; **78**: 872–877.
6. Jeevanantham V, Ntim W, Navaneethan SD, Shah S, Johnson AC, Hall B, et al. Meta-analysis of the effect of radiofrequency catheter ablation on left atrial size, volumes and function in patients with atrial fibrillation. *Am J Cardiol* 2010; **105**: 1317–1326.
7. Lombardo RMR, Reina C, Abrignani MG, Braschi A, De Castro S. Embolic stroke, sinus rhythm and left atrial mechanical function. *Eur J Echocardiogr* 2006; **7**: 401–404.
8. Masuda M, Inoue K, Iwakura K, Okamura A, Koyama Y, Kimura R, et al. The impact of atrial fibrillation ablation on left atrial function: Association with baseline left atrial function. *Pacing Clin Electrophysiol* 2012; **35**: 327–334.
9. Anselmino M, Grossi S, Scaglione M, Castagno D, Bianchi F, Senatore G, et al. Long-term results of transcatheter atrial fibrillation ablation in patients with impaired left ventricular systolic function. *J Cardiovasc Electrophysiol* 2013; **24**: 24–32.
10. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification. *Eur J Echocardiogr* 2006; **7**: 79–108.
11. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009; **22**: 107–133.
12. Blume GG, McLeod CJ, Barnes ME, Seward JB, Pellikka PA, Bastiansen PM, et al. Left atrial function: Physiology, assessment, and clinical implications. *Eur J Echocardiogr* 2011; **12**: 421–430.
13. Hoit BD. Left atrial size and function: Role in prognosis. *J Am Coll Cardiol* 2014; **63**: 493–505.
14. Vizzardi E, D'Aloia A, Rocco E, Lupi L, Rovetta R, Quinzani F, et al. How should we measure left atrium size and function? *J Clin Ultrasound* 2012; **40**: 155–166.

15. Erdei T, Dénes M, Kardos A, Mihálc A, Földesi C, Temesvári A, et al. Could successful cryoballoon ablation of paroxysmal atrial fibrillation prevent progressive left atrial remodeling? *Cardiovasc Ultrasound* 2012; **10**: 11.
16. Pump A, Di Biase L, Price J, Mohanty P, Bai R, Santangeli P, et al. Efficacy of catheter ablation in nonparoxysmal atrial fibrillation patients with severe enlarged left atrium and its impact on left atrial structural remodeling. *J Cardiovasc Electrophysiol* 2013; **24**: 1224–1231.
17. Machino-Ohtsuka T, Seo Y, Ishizu T, Yanaka S, Nakajima H, Atsumi A, et al. Significant improvement of left atrial and left atrial appendage function after catheter ablation for persistent atrial fibrillation. *Circ J* 2013; **77**: 1695–1704.
18. To ACY, Flamm SD, Marwick TH, Klein AL. Clinical utility of multimodality LA imaging: Assessment of size, function, and structure. *JACC Cardiovasc Imaging* 2011; **4**: 788–798.
19. Rodrigues ACT, Scannavacca MI, Caldas MA, Hotta VT, Pisani C, Sosa EA, et al. Left atrial function after ablation for paroxysmal atrial fibrillation. *Am J Cardiol* 2009; **103**: 395–398.
20. Lemola K, Desjardins B, Sneider M, Case I, Chugh A, Good E, et al. Effect of left atrial circumferential ablation for atrial fibrillation on left atrial transport function. *Heart Rhythm* 2005; **2**: 923–928.
21. Steel KE, Roman-Gonzalez J, O'Bryan CL 4th. Images in cardiovascular medicine: Severe left atrial edema and heart failure after atrial fibrillation ablation. *Circulation* 2006; **113**: e659, doi:10.1161/CIRCULATIONAHA.105.562959.
22. Wylie JV Jr, Peters DC, Essebag V, Manning WJ, Josephson ME, Hauser TH. Left atrial function and scar after catheter ablation of atrial fibrillation. *Heart Rhythm* 2008; **5**: 656–662.
23. Marsan NA, Tops LF, Holman ER, Van de Veire NR, Zeppenfeld K, Boersma E, et al. 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. *Am J Cardiol* 2008; **102**: 847–853.
24. Tsao HM, Hu WC, Wu MH, Tai CT, Chang SL, Lin YJ, et al. The impact of catheter ablation on the dynamic function of the left atrium in patients with atrial fibrillation: Insights from four-dimensional computed tomographic images. *J Cardiovasc Electrophysiol* 2010; **21**: 270–277.
25. Perea RJ, Tamborero D, Mont L, De Caralt TM, Ortiz JT, Berrueto A, et al. Left atrial contractility is preserved after successful circumferential pulmonary vein ablation in patients with atrial fibrillation. *J Cardiovasc Electrophysiol* 2008; **19**: 374–379.
26. Leung DY, Boyd A, Ng AA, Chi C, Thomas L. Echocardiographic evaluation of left atrial size and function: Current understanding, pathophysiologic correlates, and prognostic implications. *Am Heart J* 2008; **156**: 1056–1064.
27. Buber J, Luria D, Sternik L, Raanani E, Feinberg MS, Goldenberg I. Left atrial contractile function following a successful modified Maze procedure at surgery and the risk for subsequent thromboembolic stroke. *J Am Coll Cardiol* 2011; **58**: 1614–1621.
28. Stöllberger C, Schneider B, Winkler-Dworak M, Finsterer J. Prevention of embolic stroke by catheter ablation of atrial fibrillation. *Eur J Neurol* 2008; **15**: 1419–1420.
29. Chao TF, Lin YJ, Chang SL, Lo LW, Hu YF, Chung FP, et al. Can oral anticoagulants be stopped safely after a successful atrial fibrillation ablation? *J Thorac Dis* 2015; **7**: 172–177.
30. Murakoshi N, Aonuma K. Epidemiology of arrhythmias and sudden cardiac death in Asia. *Circ J* 2013; **77**: 2419–2431.
31. Nikitin NP, Witte KKA, Thackray SDR, Goodge LJ, Clark AL, Cleland JGF. Effect of age and sex on left atrial morphology and function. *Eur J Echocardiogr* 2003; **4**: 36–42.
32. D'Ascenzo F, Corleto A, Biondi-Zoccai G, Anselmino M, Ferraris F, di Biase L, et al. Which are the most reliable predictors of recurrence of atrial fibrillation after transcatheter ablation?: A meta-analysis. *Int J Cardiol* 2013; **167**: 1984–1989.
33. Nagaya M, Kawasaki M, Tanaka R, Onishi N, Sato N, Ono K, et al. Quantitative validation of left atrial structure and function by two-dimensional and three-dimensional speckle tracking echocardiography: A comparative study with three-dimensional computed tomography. *J Cardiol* 2013; **62**: 188–194.
34. De Groot NM, Schalij MJ. Imaging modalities for measurements of left atrial volume in patients with atrial fibrillation: What do we choose? *Europace* 2010; **12**: 766–767.
35. Kühl HP, Schreckenberger M, Rulands D, Katoh M, Schäfer W, Schummers G, et al. High-resolution transthoracic three-dimensional echocardiography: Quantitation of cardiac volumes and function using semi-automatic border detection and comparison with cardiac magnetic resonance imaging. *J Am Coll Cardiol* 2004; **43**: 2083–2090.
36. Flachskampf FA, Badano L, Daniel WG, Feneck RO, Fox KF, Fraser AG, et al. Recommendations for transoesophageal echocardiography: Update 2010. *Eur J Echocardiogr* 2010; **11**: 557–576.