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Original Paper

Clinical outcomes of left atrial circumferential ablation and box ablation for paroxysmal atrial fibrillation

Morio Ono*, Toshitaka Okabe, Wataru Igawa,
Yu Asukai, Jumpei Saito, Yuji Oyama,
Kennosuke Yamashita, Myong Hwa Yamamoto, Naoei Isomura
and Masahiko Ochiai

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Abstract

Left atrial circumferential ablation (LACa) and box ablation (BOXa) are two common treatments for paroxysmal atrial fibrillation (PAF). However, only a few studies have compared these two approaches. This study aimed to compare the clinical outcomes of these two therapeutic modalities. Patients with PAF who underwent catheter ablation were randomly assigned to either the LACa or BOXa groups and were followed up for 6 months. The primary outcomes were the rate of atrial fibrillation (AF) recurrence after 6 months and changes in the left atrial ejection fraction (LAEF) measured *via* magnetic resonance imaging from baseline to follow-up. The secondary outcomes included the frequency of supraventricular premature beats (SPBs) and short supraventricular runs (SVRs) on a 24-h electrocardiogram at follow-up. A total of 40 patients were randomly assigned to the LACa (n=21) or BOXa group (n=19). No significant between-group differences were observed in the patient characteristics and LAEF at baseline or the rate of AF recurrence at 6 months (LACa, 4.8% [1/21] vs. BOXa, 5.3% [1/19]; *P*=0.94) as well as changes in the LAEF at 3 and 6 months. However, the frequency of SPB and SVR at 6 months was significantly lower in the LACa group than in the BOXa group (0.2 [−0.2, 0.50] / 24 h vs. 0.8 [0.5, 1.2] / 24 h, *P* =0.01; 2.2 [−4.2, 8.7] / 24 h vs. 11.9 [4.8, 18.9] / 24 h, *P*=0.04, respectively). Although the rates of AF recurrence and changes in the LAEF were comparable between the LACa and BOXa groups, the higher incidence of SPBs and SVRs at 6 months in the BOXa group suggests that BOXa provided no advantage in the treatment of PAF patients.

Key words: atrial fibrillation, catheter ablation, left atrium function, recurrence rate, supraventricular premature beats

Introduction

The prevalence of atrial fibrillation (AF) is increasing globally[1]. Patients with AF are known to be at an increased risk of ischemic stroke and heart failure, with the latter occurring in approximately 40% of patients[2–4]. In patients with AF, catheter ablation is more effective in reducing cardiovascular events and mortality than antiarrhythmic drug therapy[5, 6]. These findings have led to the greater use of catheter ablation for AF, particularly in patients with paroxysmal AF (PAF)[2–6]. However, the most effective catheter ablation for treating PAF remains unknown. In addition, the effects of catheter ablation on left atrial function, including ejection fraction, remain unclear. Left atrial circumferential ablation (LACa) and box ablation (BOXa) are two recently used methods for the treatment of PAF[7, 8]. Previous studies with small cohorts reported that both strategies improve acute success and procedural complication rates[9, 10]. However, few studies have directly compared the two approaches. Therefore, this study aimed to evaluate the efficacy, safety, and effect on the atrial function of LACa and BOXa in the

* Corresponding author
✉ Morio Ono, MD
morio.ono@gmail.com

Division of Cardiology, Showa University Northern Yokohama Hospital, 35-1, Chigasaki-Chuo, Tsuzuki-Ku, Yokohama, Kanagawa 224-8503, Japan.

management of PAF.

Subjects and methods

Study design

This study was a prospective, randomized, single-blind, single-center trial (Clinical Trial Registration: UMIN-CTR, UMIN000028470) that included patients with PAF who were recruited between October 2017 and August 2018. This study was conducted in accordance with the Helsinki Declaration and was approved by the Institutional Review Board of Showa University Northern Yokohama Hospital (approval number: 17H032). Written informed consent was obtained from all participants. We planned 80 cases involving the study of 20 registrants who calculated their left atrial ejection fraction (LAEF) *via* magnetic resonance imaging because there had been no previous research (MRI). However, due to the limited capacity of MRI in our hospital, the registration was completed with 40 cases[11].

Patients (aged 20–80 years) diagnosed with PAF who were referred for catheter ablation due to refractory symptoms as well as those with *de novo* PAF were included in the study Refractory symptoms were defined as the failure of symptom resolution after using more than one class I or Ⅲ antiarrhythmic drugs or beta-blockers. Patients with the following characteristics were excluded: history of congenital heart disease, contraindications to MRI, and requiring hemodialysis treatment. After enrollment, the patients were randomly assigned to undergo LACa or BOXa. The flow chart of the study is presented in Figure 1. Patients that do not have sinus rhythm when analyzed *via* MRI are not appropriate for the accurate measurement of the LAEF. Similarly, if it is not sinus rhythm, the values of 24-h Holter monitor and biomarker would be inappropriate. Therefore, the cases with AF recurrence after catheter ablation were excluded from the analyses of MRI, 24-h Holter monitor, and biomarker.

Interventions

An electro-anatomical mapping system (CARTO® 3, Biosense Webster, CA, USA; EnSite™ NavX™, Abbott, IL, USA; EnSite™ Velocity, Abbott, IL, USA) was created using a three-dimensional model of the left atrium (LA). The procedure started with a transeptal puncture performed under fluoroscopic and intracardiac echocardiographic guidance. A circulatory mapping catheter (Inquiry™ AFocusII™, Irvine Biomedical Inc., CA, USA; or PentaRay®, Biosense Webster, Inc., CA, USA) was placed inside the pulmonary veins, and a wide antral ablation line was created around each pair of the ipsilateral pulmonary veins using a radiofrequency ablation catheter (TactiCath™, Abbott, IL, USA; or THERMO COOL SMARTTOUCH®, Biosense Webster, CA, USA: 30–35 W, 30–40 s, 10–20 g). LACa was defined as completion of the aforementioned procedure. In the BOXa group, after complete pulmonary vein isolation, a "roofline" was created between the top of each contralateral set of lesions, and a "floor line" closed the posterior wall that connected the base of each set of the contralateral lesion in a "box" fashion. The endpoints of both procedures were complete isolation of the posterior wall, dissociation of the potentials in the posterior wall using a high-density mapping catheter (inquiry™ AFocusII™, Irvine Biomedical Inc., CA, USA; or PentaRay®, Biosense Webster, Inc., CA, USA), and the inability to capture the atrium by 10-V pacing in the posterior wall after regaining sinus

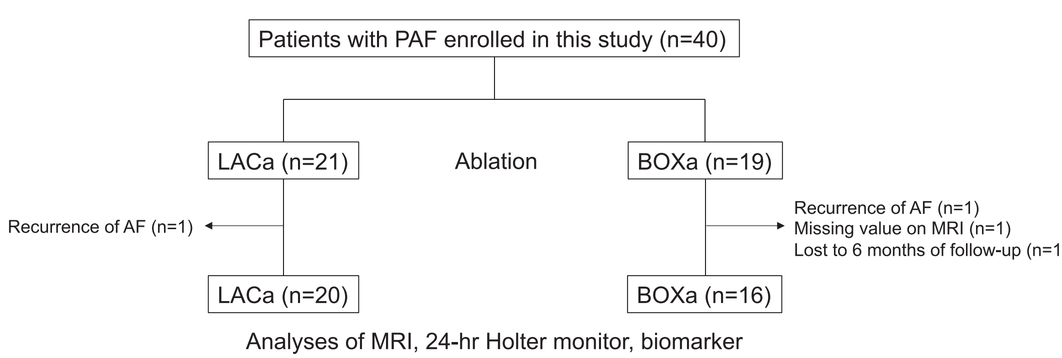

Fig. 1. Study flowchart
AF, atrial fibrillation; BOXa, box ablation; LACa, left atrial circumferential ablation; MRI, magnetic resonance imaging

rhythm. Power titration was performed according to the esophageal temperature, and radiofrequency lesions were stopped when ≥ 39° was reached.

Outcome measures

The primary outcomes in the comparison of BOXa and LACa were the rate of AF recurrence (lasting more than 30 s) at 6 months and changes in the LAEF measured *via* MRI from baseline to follow-up. The secondary outcome was the frequency of supraventricular premature beats (SPBs) and short supraventricular runs (SVRs). The laboratory data, frequency of SPBs and SVRs, and LAEF using MRI were evaluated at baseline and 3 and 6 months after the procedure. Early recurrence of AF within the first 90 days after ablation is not considered recurrence, as it may result from inflammation or incomplete lesion healing, which is common and is not necessarily predictive of long-term outcomes[12]. Recurrent arrhythmias managed with antiarrhythmic drugs or cardioversion within the blanking period were therefore excluded from the number of AF recurrence. The frequency of SPBs was defined as the SPB / total heart rate on a 24-h Holter monitor. SVRs were defined as >3 consecutive supraventricular beats with an accelerated cycle length lasting <30 s[13].

The patients were placed in a supine position, and cardiac MRI was performed using a 3.0-T scanner (GE Medical Systems, Milwaukee, WI, USA). Following scan localization, electrocardiography-gated cine images of the heart were obtained in two standard long axes and multiple short-axis slices, with a slice thickness of 8 mm and an interslice distance of 2 mm from the base to the apex of the heart. All images were analyzed offline using Ziostation 2 (Ziosoft Inc., Tokyo, Japan). The LA maximum was defined as the frame immediately preceding the mitral valve opening. We defined LA maximum as the largest possible left atrial diameter maximum (LAD maximum). The frame immediately following mitral valve closure was defined as the LA minimum. Two experienced operators measured the volumes in both two- and four-chamber views. The LA's endocardial border was manually traced. The anterior border, excluding the LA appendage, was at the mitral annular plane, whereas the posterior border was at the ostia of the pulmonary veins. The LA volumes were calculated using the area-length method (volume $=0.85\times \text{area}^2/\text{length}$), and the LAEF was calculated using the formula: [(LA max−LA min) / LA max] ×100%. In addition, the LA total emptying volume was calculated (reservoir function) using LA max−LA min, and the LA conduit volume was calculated using LV stroke volume−LA total emptying volume[14].

Study follow-up

Hospital visits were scheduled at 3 and 6 months following the ablation procedure. At each visit, the medical history, MR images, blood examination, and 24-h Holter monitoring records were obtained. All follow-up assessments were performed by study personnel who were blinded to the treatment assignments.

Statistical analysis

We were unable to calculate the minimum number of patients needed for this study as there is limited data on the LA function in patients with AF who have undergone catheter ablation. Therefore, we enrolled 40 patients as per our procedure volume. The primary hypothesis was that BOXa using radiofrequency ablation performed worse than LACa in terms of LAEF.

Continuous variables were expressed as medians and interquartile ranges (IQRs), representing the 25th to 75th percentiles of the distribution data, and compared using the Mann-Whitney U test. Categorical variables were expressed as percentages and compared using the chi-squared test or Fisher's exact test, depending on the situation. Multiple linear regression analysis was conducted to examine the predictors of SVRs, including variables when $P<0.10$ was obtained for the single regression analysis or if the relationship was demonstrated by previous studies. The regression coefficient and 95% confidence interval were calculated. Multicollinearity was used to assess the variance inflation factor (analysis of variance). Statistical significance was set to $P<0.05$. All data were analyzed using the JMP software (SAS Institute, Inc., Cary, NC, USA).

Results

This study included a total of 40 patients (LACa: 21, BOXa: 19). No significant between-group differences were observed in the patient characteristics or baseline LAEF (Table 1). Among the procedure variables, only ablation time significantly differed between the two groups; ablation time was significantly shorter in patients treated with LACa than in those treated with BOXa (43.8 [39.5, 47.9] min vs. 49.1 [44.3, 53.8] min, $P=0.047$). Notably, the AF recurrence rate at 6 months after the procedures

Table 1. Patient and procedural characteristics

	LACa (n=21)	BOXa (n=19)	*P*-value
Age, years	65.3 [61.3, 69.2]	68.3 [62.7, 73.7]	0.35
Female	7 (33.3)	5 (26.3)	0.62
BMI, kg/m^2	22.6 [20.8, 24.4]	22.4 [21.1, 23.6]	0.83
Hypertension	10 (47.6)	9 (47.4)	0.98
Diabetes	4 (19.1)	3 (15.8)	0.78
Hyperlipidemia	9 (42.9)	7 (36.8)	0.69
Smoking	9 (42.9)	5 (26.3)	0.27
Alcohol intake history	5 (23.1)	4 (21.1)	0.83
$CHADS_2$ score	0.8 [0.3, 1.2]	1.4 [0.9, 1.8]	0.09
Heart failure	1 (4.8)	1 (5.3)	0.94
LVEF, %	66.8 [63.5, 69.9]	63.1 [56.8, 69.5]	0.24
Hb, mg/dl	14.1 [13.5, 14.8]	14.3 [13.6, 15.0]	0.74
Creatinine, mg/dl	0.9 [0.07, 0.8]	0.8 [0.08, 0.7]	0.49
BNP, pg/ml	61.3 [48.1, 172.1]	110.1 [40.1, 81.9]	0.06
Procedural characteristics			
Radioscopic time, min	78.5 [68.1, 88.9]	73.7 [62.0, 85.4]	0.54
Dose radiation, mGy	517 [360, 638]	438 [302, 574]	0.38
Procedure time, min	214 [196, 232]	217 [197, 238]	0.79
Ablation time, min	43.8 [39.5, 47.9]	49.1 [44.3, 53.8]	0.047

Values are expressed as medians, interquartile ranges, or no. (percentage)
BOXa, box ablation; BMI, body mass index; Hb, hemoglobin; LACa, left atrial circumferential ablation; LVEF, left ventricular ejection fraction

was similar in both groups (LACa, 4.8% [1/21] vs. BOXa, 5.3% [1/19]; *P*=0.94). The LAEF at 3 and 6 months also did not significantly differ between the LACa and BOXa groups (26.4 [23.1, 29.7]% vs. 25.0 [20.2, 29.8]%, *P*=0.60; 25.4 [22.8, 29.7]% vs. 25.9 [21.1, 30.8]%, *P*=0.85, respectively) (Table 2, Figure 2).

At 3 months, no significant difference was observed in the LAEF changes between the patients treated with LACa and those treated with BOXa at 3 months (0.1 [−3.9, 4.1]% vs. 1.2 [−5.0, 7.4]%, *P*=0.75) and at 6 months (−0.8 [−5.8, 4.1]% vs. 2.1 [−3.2, 7.5]%, *P*=0.41), respectively (Table 2, Figure 3).

The brain natriuretic peptide level at 3 months (32.0 [18.6, 45.4] pg/ml vs. 46.2 [27.4, 65.0] pg/ml, *P*=0.16) and 6 months (38.2 [20.7, 43.3] pg/ml vs. 41.9 [23.4, 60.4] pg/ml, *P*=0.72) were not significantly different between the two groups. LAD maximum at 3 months (40.4 [39.0, 41.9] mm vs. 39.9 [38.3, 41.4] mm, *P*=0.58) and 6 months were not significantly different between the two groups (39.6 [38.2, 41.0] mm vs. 39.8 [38.2, 41.3] mm, *P*=0.86). At 6 months, the frequencies of SPBs (0.2 [−0.2, 0.50]/24 h vs. 0.8 [0.5, 1.2]/24 h, *P*=0.01) and SVRs (2.2 [−4.2, 8.7]/24 h vs. 11.9 [4.8, 18.9]/24 h, *P*=0.04) were significantly lower in the LACa group than in the BOXa group (Table 2). Multiple regression analysis revealed that BOXa was an independent predictor of the frequency of SVRs (regression coefficient=18, 95% CI, 2.37-33.7, *P*=0.03) (Table 3).

Discussion

This study compared the efficacy of LACa and BOXa in the treatment of PAF. There was no significant differences between the LA function and AF recurrence rate in the two treatment modalities. However, the frequencies of SPBs and SVRs were significantly lower in the LACa group than in the BOXa group.

Atrial contraction increases blood flow (∼20%-30%) across the mitral valve, thereby contributing to the total diastolic volume. Inadequate filling of the left ventricle due to loss of atrial contraction can reduce cardiac output. Considering this, it is important to identify the effect of radiofrequency ablation on the LA function of patients with AF. Our findings indicated no changes in the LAEF of patients pre- and post-ablation. Similarly, changes in the LAEF were similar between the two groups. A lack of posterior wall contractility is thought to be

Table 2. Primary and secondary outcomes in the LACa and BOXa groups

	LACa (n=20)	BOXa (n=16)	*P* Value
LAEF at baseline, %	26.3 [21.8, 30.7]	23.8 [18.0, 29.8]	0.46
LAEF at 3 months, %	26.4 [23.1, 29.7]	25.0 [20.2, 29.8]	0.60
LAEF at 6 months, %	25.4 [22.8, 29.7]	25.9 [21.1, 30.8]	0.85
ΔLAEF (3 months-baseline), %	0.1 [−3.9, 4.1]	1.2 [−5.0, 7.4]	0.75
ΔLAEF (6 months-baseline), %	−0.8 [−5.8, 4.1]	2.1 [−3.2, 7.5]	0.41
LAD maximum at baseline	40.7 [38.7, 42.7]	41.7 [39.6, 43.9]	0.48
LAD maximum at 3 months, mm	40.4 [39.0, 41.9]	39.9 [38.3, 41.4]	0.58
LAD maximum at 6 months, mm	39.6 [38.2, 41.0]	39.8 [38.2, 41.3]	0.86
BNP at 3 months, pg/ml	32.0 [18.6, 45.4]	46.2 [27.4, 65.0]	0.16
BNP at 6 months, pg/ml	38.2 [20.7, 43.3]	41.9 [23.4, 60.4]	0.72
3-month SPB, /day	0.3 [0.02, 0.5]	0.48 [0.2, 0.7]	0.18
3-month SVR, /day	3.5 [−0.1, 7.1]	8.5 [4.4, 12.5]	0.06
6-month SPB, /day	0.2 [−0.2, 0.50]	0.8 [0.5, 1.2]	0.01
6-month SVR, /day	2.2 [−4.2, 8.7]	11.9 [4.8, 18.9]	0.04

Values are expressed as medians and interquartile ranges
LAEF, left atrial ejection fraction; ΔLAEF, changes in the LAEF; LACa, left atrial circumferential ablation; BNP, brain natriuretic peptide; BOXa, BOX ablation; PAC, premature atrial contraction; LAD, left atrium diameter measured by MRI

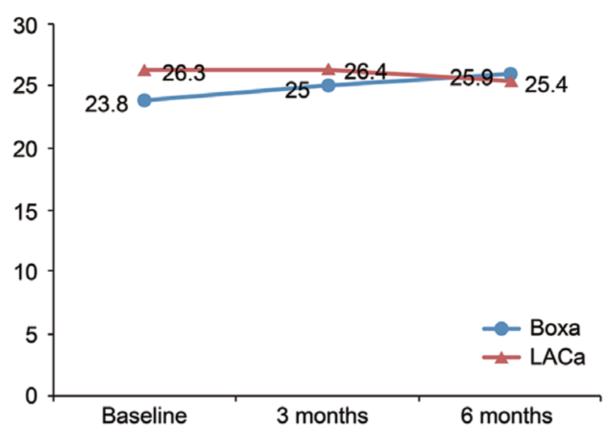

Fig. 2. Differences in the LAEF between the BOXa and LACa groups
(Red) LAEF of the LACa group over 6 months; (blue) LAEF of the BOXa group over 6 months
BOXa, box ablation; LACa, left atrial circumferential ablation; LAEF, left atrial ejection fraction

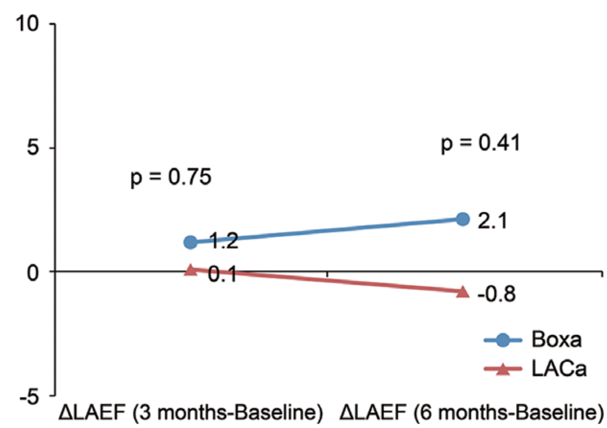

Fig. 3. Differences in the Δ LAEF between the BOXa and LACa groups
(Red) Change in the LAEF of the LACa group over 6 months; (blue) change in the LAEF of the BOXa group over 6 months
BOXa, box ablation; LACa, left atrial circumferential ablation; LAEF, left atrial ejection fraction

Table 3. Multivariate regression analysis of the relations between the frequency of short supraventricular runs (SVRs) and variables

Covariate	Regression coefficient	95% Confidence interval	*P*-value
Age, years	1.41	[−0.34, 3.15]	0.11
Female	6.98	[−9.56, 23.52]	0.39
BNP at baseline, pg/ml	−0.17	[−0.36, 0.01]	0.07
BOXa	18.0	[2.37, 33.7]	0.03
LAD maximum at 6 months, mm	1.64	[−4.03, 7.32]	0.56

BNP, brain natriuretic peptide; BOXa, BOX ablation; LAD, left atrium diameter caused by a small area of ablation or an anatomic reason during BOXa. No significant differences were observed in the biomarkers for the LA wall stress, which was consistent with the findings of the LAEF on cardiac MRI. We removed the LAA during the LAEF measurement. The reason for this is that the ejection fraction of LAA cannot be accurately measured well *via* MRI due to technical issues. Thus, our study did not reveal the impact of LAA on LAEF.

The rate of AF recurrence was comparable between the two groups. BOXa may be associated with a reduction in AF recurrence in patients with persistent AF[15]. On the contrary, Kim *et al.* demonstrated the inferiority of BOXa linear ablation in addition to LACa in reducing the recurrence rate in patients with PAF[16]. Their results were different from our study results. We thought that the causes were the short follow-up period of 6 months and the small study population. However, long-term follow-up may give different results. Furthermore, we thought that the roof and floor lines for BOXa may reconnect to LA. Thomas *et al.* reported that linear ablation (BOXa and anterior linear ablation) in addition to LACa did not improve the clinical outcomes in patients with PAF because they reported that the complete bidirectional conduction block rate was 68.0% in the linear ablation[17].

At 6 months postoperatively, the frequencies of SPBs and SVRs were significantly higher in patients treated with BOXa than in those treated with LACa in our study result. We expected the SPBs and SVRs to decrease if they were the perfect lines for all BOXa cases, because the initial box lesion was thought to generate atrial tachycardia (AT) through electrical gaps. Thomas *et al.* reported that the roofline often becomes the major problem area for creating posterior LA isolation due to the deeper muscle bundles on the roof[17]. Furthermore, another study found that the floor line was a major impediment to achieving posterior LA isolation[18]. The major recurrence sites at the floor line were adjacent to the esophagus; to avoid esophageal injury, radiofrequency energy was not delivered to the LA sites in contact with the esophagus. Choi *et al.* suggested that the SPBs and SVRs were associated with an increase in the rate of AF recurrence[19]. AT is common after ablation; it is symptomatic and refractory to antiarrhythmic medications[20, 21]. Furthermore, previous studies suggested that an electrical gap along the ablation line resulted in a conduction delay in the LA, leading to an excitable gap that might present as macro-reentrant AT[22, 23]. An incomplete conduction block of linear ablation increases the risk of recurrent AT[24]. Our study found no benefit from additional ablation, and the cause was unknown. Similarly, Atul Verma *et al.* reported that among patients with persistent AF, they found no reduction in the recurrent rate of AF when either linear ablation (left atrioventricular roof+mitral valve annulus) or ablation of complex fractionated electrograms was performed in addition to LACa[25]. Atul Verma *et al.* reported that a wider range of ablation was incompletely line-ablated, and an additional ablation could lead to the emergence of new iatrogenic areas of arrhythmia development[25]. In a report comparing LACa+left atrial linear ablation (left atrioventricular roof+mitral valve annulus) and LACa in patients with PAF, extensive line ablation for electrically normal AF was found to increase iatrogenic arrhythmias and negate the benefits of reduced recurrence rates of AF[26]. Our study also attributed the increase in SVB SVR to the emergence of new iatrogenic areas of arrhythmia caused by incomplete line ablation gap and unnecessary incomplete additional ablation. It has also been reported that at 6 months after ablation, both frequent and long PAC runs are independent predictors of late recurrence[27]. Our long-term follow-up findings could have influenced the AF recurrence rates.

Limitation

This research has some limitations. First, the study was conducted at a single center with a small cohort, which may have limited the power to detect associations and the ability to control confounders in the multivariate models. Second, a universal method for measuring cardiac MRI has not been established; therefore, inconsistencies in the results of cardiac MRI may be observed in each measurement method. Finally, there is no established cut-off point regarding the frequency of SPBs that is considered pathological.

Conclusion

The treatment of PAF with LACa may be more beneficial than the BOXa treatment and may not require additional ablation. Further studies are required to confirm the effects of each catheter ablation strategy on the LA function and the recurrence of atrial arrhythmias in patients with PAF.

Acknowledgments

W.I., Y.A., J.S., Y.O., K.Y., N.I., and M. Ochiai treated the patients and collected the data and helped draft the manuscript. M.Y. helped perform the statistical analysis. M.Ochiai. N.I. T.O. and M.Ono participated in the study design and coordination and helped draft the manuscript. M.Ono and T.O. participated in the study design and wrote the manuscript. All authors have read and approved submission of the manuscript.

Conflict of interest disclosure

The authors have no competing interests to declare.

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