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【 ORIGINAL ARTICLE 】

Comparison of Radiofrequency and Cryoballoon Pulmonary Vein Ablation for the Early and Late Recurrence of Atrial Fibrillation

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Abstract:

Objective Early recurrence (ER) after pulmonary vein isolation (PVI) for atrial fibrillation (AF) is expected to resolve within the recommended 3-month blanking period, irrespective of the ablation device used. To compare the occurrence and relationship of AF within the blanking period and subsequent late recurrence (LR) with radiofrequency (RF) and cryoballoon (CB) ablation.

Methods A retrospective analysis of 294 patients (mean age=62±9, 70.0% male) undergoing PVI for drug-refractory paroxysmal AF was done. After categorizing the patients into the RF group (n=152) and the CB group (n=142), a group-wise comparison was done to investigate the impact of ER on LR throughout a 2-year follow-up.

Results The groups were similar regarding the occurrence of ER (RF=22.4%, CB=24.6%, p=0.62), while LR was significantly higher in the RF group (p=0.003). ER was associated with LR in the RF group (p< 0.01) but not in the CB group (p=0.08), while a significant independent association with an increased LR risk was observed [hazard ratio (HR) 6.12; 95% confidence interval (CI) 3.56-10.51, p<0.01]. RF ablation also significantly increased the risk of LR (HR=2.93; 95% CI=1.64-5.23, p<0.01).

Conclusion A recurrence of atrial arrhythmia is more frequent with RF-PVI than with CB-PVI for patients with paroxysmal AF. ER and RF-ablation are strong predictors for LR after the 3-month blanking period.

Key words: atrial fibrillation, blanking period, radiofrequency ablation, cryoballoon ablation

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Introduction

Pulmonary vein isolation (PVI) is an acclaimed treatment alternative for symptomatic drug-refractory atrial fibrillation (AF) (1, 2). Besides conventional radiofrequency (RF) ablation, various new techniques have recently been developed, including cryoballoon (CB) ablation (3-5). However, the early recurrence (ER) of AF is common after PVI despite recent technical advances, hence, a standardized blanking period of three months is recommended (2, 3, 6-8) as recurrence during this period is presumed to neither affect nor induce a late recurrence (LR) (9-11). The mechanism underlying an ER of AF after PVI through RF is affected by multiple factors (12-17), including inflammatory responses to myocardial injury, delayed scar maturation, and changes in the cardiac autonomic function, yet the detailed mechanism for this remains to be elucidated. Subsequently, the cryoballoon technique (CB-PVI) was introduced as a simpler one-shot device for PVI of AF and it provides a comparable blanking period of three months (3, 4, 18). Furthermore, recent studies have reported that ER is a predictor of LR after either technique, RF (13, 19) and CB (20, 21). However, there are limited reports directly comparing these ablation techniques in terms of the relationship between ER and LR after PVI (22). Therefore, the present study aims to compare

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the two ablation techniques, RF and CB, vis-à-vis the effect of ER on LR after each technique.

Materials and Methods

Patient population

The retrospective medical records for 294 consecutive patients of symptomatic paroxysmal AF, who had undergone their first PVI between October 2016 and May 2018 at the Research Institute for Brain and Blood Vessels, Akita, Japan, were collected and analyzed. Those with persistent and permanent AF or who had previously undergone catheter ablation for AF were excluded. Since this was a retrospective study, the choice of device was entirely left to the operator. According to the medical records, RF-PVI was selected in cases of contrast media allergy on preoperative computed tomography (CT), a large pulmonary vein diameter, and a common trunk of left pulmonary vein. This study protocol was approved by the Research Review Board of our Research Institute for Brain and Blood Vessels, Akita, Japan. Informed consent was obtained in the form of opt-out on the website. Those who rejected were excluded.

Preprocedural management

Transesophageal echocardiography was performed in all patients three days before the ablation to ensure the absence of a left atrial thrombus. The pulmonary vein anatomy was confirmed via contrast-enhanced CT. All antiarrhythmic drugs were discontinued at least five half-lives before ablation and oral anticoagulants were prescribed to all patients at least one month before the procedure.

Ablation procedure

The right femoral vein and left median cubital vein of the forearm were used to gain vascular access. A 6 Fr 20-pole steerable catheter (BeeAT, Japan Lifeline, Tokyo, Japan), capable of recording from three sites simultaneously, was inserted through the left median cubital vein and placed into the coronary sinus, the right atrium, and the superior vena cava for pacing, recording, and internal cardioversion (23). An intracardiac echocardiography (ICE) probe (AcuNav or SoundStar, Biosense Webster, Diamond Bar, USA) was placed on the right atrial septum via the femoral vein. Transseptal access to the left atrium was established using an RF needle (Baylis Medical, Montreal, Canada) and an 8 Fr or 8.5Fr long sheath (SL0, Abbott, MN, USA) under fluoroscopic and ICE guidance. During the procedure, a state of systemic anticoagulation was ensured through repetitive intravenous heparin administration to maintain an activated clotting time of 300-350 seconds. A 7Fr esophageal catheter (Esophastar, Japan Lifeline) was inserted nasally and advanced into the esophagus, posterior to the left atrium, under fluoroscopic guidance. Esophageal temperature was continuously monitored during the ablation and the application was discontinued if the temperature reached 39℃ (RF-PVI) or 15℃ (CB-PVI).

RF-PVI procedure

Through the single transseptal access to the left atrium, an 8.5Fr deflectable guide sheath (Symmetry, Century Medical, Tokyo, Japan) was advanced into the left atrium using a guidewire (inserted prior through the first puncture site) for reference. The irrigated-tip ablation catheter with contact-force-sensing technology (ThermoCool SmartTouch-SF, Biosense Webster), along with a multipolar mapping catheter (Pentaray, Biosense Webster) were placed in the left atrium via the 8.5Fr deflectable sheath and the 8.0Fr long sheath, respectively. RF ablation was performed using a 3D electroanatomical mapping system (CARTO3 system, Biosense Webster) and the RF energy was delivered anatomically to eliminate local electrograms within the pulmonary veins. Wide area circumferential PVI was performed in power-controlled mode. RF application was limited to 30 W at the posterior wall and to 30 W at the anterior wall. The target force-time integral (FTI) was 300 gs for the posterior wall and 450 gs for the anterior wall. The target ablation index (AI) was 380 for the posterior wall and 400 to 450 for the anterior wall. We did not set a target "inter-lesion distance," but we made sure that a 4 mm tag would not leave a gap between the neighboring ablation points. A high dose of isoproterenol challenge with 20 mg adenosine triphosphate (ATP) was given for each vein to assess for dormant conduction. If dormant conduction was induced, additional RF energy was applied in order to eliminate the dormant PV conduction. The acute procedural end point was defined as the absence or dissociation of all PV potentials, as confirmed by a bi-directional block using a circular mapping catheter after a 30 minute waiting period and complete PV disconnection reconfirmed by repeat ATP injections under continuous isoproterenol infusion. We also attempted to ablate non-PV frequent atrial premature contractions, including the superior vena cava, if they triggered AF. Concomitant ablation was performed for previously documented cavotricuspid isthmus-dependent atrial flutter (AFL). We did not perform atrial rapid pacing, empiric linear ablation or defragmentation.

CB PVI procedure

After obtaining a single transseptal puncture (similar as above), the transseptal sheath was exchanged over a guidewire for a 15Fr steerable sheath (FlexCath Advance, Medtronic, Minneapolis, USA). A spiral inner lumen mapping catheter (Achieve, Medtronic) preceded the balloon and brought it to each pulmonary vein. A 28 mm second-generation CB (Arctic Front Advance, Medtronic) was inflated and positioned at the ostium. The degree of sealing was confirmed using contrast-medium injected from the distal tip of the balloon. Ablation was performed with a single 240-second freeze for the left upper pulmonary vein and 180-second for other veins. An additional application was done for another 180 seconds, if necessary. If electrical iso-

lation was not achieved after 3 applications per vein, touch-up ablation for 150 seconds was performed using a cryo-catheter (Freezer Max, Medtronic) for each application. As in the RF group, entrance and exit block was also confirmed. However, because of the low incidence of dormant conduction after CB isolation in previous studies (24, 25), only a high-dose isoproterenol challenge was performed, and dormant conduction was not confirmed by ATP.

Post-ablation Follow-up

Recurrence, for this study, was defined as documented atrial arrhythmia (AF, AFL, and atrial tachycardia) lasting > 30 seconds with or without symptoms after a single ablation procedure. We defined an ER of atrial arrhythmia as an episode within 3 months after ablation, and LR as these episodes after the blanking period was over.

All patients were monitored for 48 hours after the procedure in the hospital and thereafter were discharged, if clinically stable. Patients visited the cardiology clinic monthly or every alternate month, and our hospital at 3, 6, 12, and 24 months postoperatively for further examination. Additionally, they maintained a self-recorded notebook for daily blood pressure and pulse readings using a home blood pressure monitor. Whenever the patient had an irregular or rapid pulse, they visited a primary care physician or our hospital, where ECG and Holter monitoring was done each time. Oral anticoagulants were prescribed for all patients for at least three months post-procedure, while those with a $CHADS_2$ score of ≥1 continued oral anticoagulant regardless of the recurrence of AF. Antiarrhythmic drugs were not resumed after ablation if there was no atrial arrhythmia. However, in the case of recurrence of atrial arrhythmias within 3 months post-procedure, antiarrhythmic drugs were resumed at the attending physician's discretion and discontinued after 3 months; if the recurrence occurred while taking antiarrhythmic drugs after 3 months, it was included in LR. In patients who underwent a redo procedure, the incidence of PV reconduction was compared between the two groups.

Outcomes

The primary outcome was LR of atrial arrhythmia in patients having an ER after the ablation procedure. The secondary outcomes include LR with and without ER, risk factors for LR, and procedure-related complications during the follow-up period.

Statistical analysis

Age, BMI, and echocardiographic parameters were expressed the mean±SD. Categorical variables are expressed as absolute and relative frequencies. The $CHADS_2$ and CHA_2DS_2-VASC scores have been described using median and 25%, 75% percentile, followed by absolute and percentage for each score by each group. Categorical variables were compared using either the chi-square test or the Fisher's exact test, as appropriate. The Kaplan-Meier analysis followed by log-rank comparison was used to estimate the event-free survival after the blanking period, and the Cox proportional hazards regression was used to compute hazard ratios. All statistical analyses were performed using EZR on the R-commander version 1.52 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R version 4.02 (The R Foundation for Statistical Computing, Vienna, Austria). It is a modified version of the R-commander designed to add statistical functions frequently used in biostatistics (26).

Results

The median follow-up period of this study was 734 days [range=614-744 days]. Of the 294 patients (age=62±9, 70.0% male), 152 patients had undergone RF ablation, while the other 142 patients underwent CB ablation. The baseline clinical characteristics of all patients are shown in Table 1. The two groups were similar in terms of baseline characteristics like age, gender, underlying disease, and $CHADS_2$ score. On comparing the preprocedural echocardiography for both groups, no significant differences were observed in terms of the ejection fraction, and the left atrial diameter, and volume (p=0.64, 0.49, and 0.16, respectively). Overall, 23.5% of patients had ER of AF after the PVI within the blanking period, which was also similar when comparing the groups (RF=22.4% and CB=24.6%).

No severe complications, such as procedure-related death, atrial-esophageal fistula, or stroke, except for one case of cardiac tamponade requiring pericardiocentesis, were observed. One patient in the CB group had a 75% pulmonary-vein stenosis in the early post-ablation period, which improved to about 25% stenosis after one year during follow-up. Four patients had femoral puncture-site hematomas, but none of them required vascular intervention or blood transfusion (Table 2).

The cumulative LR rate in all patients was analyzed by Kaplan-Meier curves (Fig. 1). There were more recurrences in the RF group than the CB group, with a significant difference observed using the log-rank test (p=0.003). The two groups had statistically significant differences (p<0.001) in terms of recurrences, 34 patients in the RF group developed ER compared to 35 in the CB group (Fig. 2). The RF group had a 50% recurrence rate within 2 months after the blanking period (Fig. 2).

We also compared each group for LR in patients with or without ER (Fig. 3). In the RF ablation group, the incidence of recurrences after ER was statistically and clinically significant (Fig. 3A). In contrast, in the CB group, patients who had ER seemed to have more recurrences than those who did not, but the difference was not statistically significant (Fig. 3B).

Furthermore, according to a univariate Cox regression analysis, LR was more likely to occur after ER with a hazard ratio (HR) of 5.25 [95% confidence interval (CI)=3.08-8.94, p<0.01] and in RF ablation with a HR of 3.0 (95% CI =1.30-4.07, p<0.01) (Table 3). A multivariate analysis was

Table 1. Baseline Clinical Characteristics of the Study Population.

	All	RF group	CB group	p value
No. of patients	294	152	142	
Age	62±9	61±9	62±9	0.84
Male	206 (70.0)	99 (65.1)	107 (75.4)	0.06
BMI	23.7±3	23.8±3	23.6±3	0.72
Hypertension	141 (48.0)	72 (47.4)	69 (48.6)	0.83
Diabetes mellitus	40 (13.6)	19 (12.5)	21 (14.8)	0.57
Congestive heart failure	17 (5.8)	8 (5.3)	9 (6.3)	0.69
Renal failure	12 (4.1)	4 (2.6)	8 (5.6)	0.19
Liver dysfunction	12 (4.1)	6 (3.9)	6 (4.2)	0.90
Coronary artery disease	29 (9.9)	14 (9.2)	15 (10.6)	0.70
Stroke/TIA	20 (6.8)	10 (6.6)	10 (7.0)	0.88
SAS (AHI ≥15 and/or CPAP)	57 (19.4)	32 (22.5)	25 (16.4)	0.24
High consumption of alcohol[1]	23 (7.8)	13 (8.6)	10 (7.0)	0.67
$CHADS_2$ score	1 [0, 1]	1 [0, 1]	1 [0, 1]	0.47
0	122 (41.4)	65 (42.8)	57 (40.1)	
1	118 (40.1)	62 (40.8)	56 (39.4)	
2	41 (13.9)	19 (12.5)	22 (15.5)	
≥3	13 (4.4)	6 (4.0)	7 (4.9)	
CHA_2DS_2-VASc score	1 [0, 2]	1 [0, 2]	1 [0, 2]	0.44
0	82 (27.9)	43 (28.3)	39 (27.5)	
1	93 (31.6)	49 (32.2)	44 (31.0)	
2	60 (20.4)	36 (23.7)	24 (16.9)	
3	34 (11.6)	14 (9.2)	20 (14.1)	
≥4	25 (8.5)	10 (6.9)	15 (10.5)	
Ejection fraction (%)	66.6±8	65.8±8	67.1±6	0.64
LA diameter (mm)	37.4±5	37.2±5	37.7±5	0.49
LA volume (mL)	45.6±15	44.4±15	46.8±15	0.16
Early recurrence	69 (23.5)	34 (22.4)	35 (24.6)	0.62

Values are presented as mean±SD or n (%). The $CHADS_2$ and CHA_2DS_2-VASC scores have been described using median and 25%, 75% percentile.

SAS: sleep apnea syndrome, AHI: apnea hypopnea index, CPAP: continuous positive airway pressure, LA: left atrium, 1: consumption of alcohol ≥60 g/day

performed using age, ER, and RF with a p<0.1 in a univariate analysis. The multivariate Cox regression analysis showed ER to be significantly and independently associated with an increased LR risk with a HR of 6.12 (95% CI=3.56-10.51, p<0.01). RF ablation, also, significantly increased the risk of LR with a HR of 2.93 (95% CI=1.64-5.23, p<0.01) (Table 3).

The types of recurrent arrhythmias are shown in Table 4. In both groups, most of the patients in both ER and LR were in AF, with few AFL or atrial tachycardia. One patient in the RF group who had a frequent short run on premature atrial contraction (PAC), was symptomatic, and thus was started on antiarrhythmic drugs during the blanking period was included in the ER. Three months later, the antiarrhythmic drugs were discontinued, but the patient underwent a redo procedure for a repetitive short run of PAC due to electrically reconnected PV and was thus included in the LR.

In the LR group, 32 patients (84.2%) in the RF group and 15 patients (88.2%) in the CB group had a second ablation procedure using RF catheter. PV reconduction was observed in 28 patients (87.5%) in the RF group and 12 patients (80.0%) in the CB group, but there was no difference between the two groups (p=0.66). There were 35 patients with only PV reconnections (RF 25, CB 10), 7 patients with only non-PV triggers (RF 4, CB 3), and 5 patients with both PV reconnections and non-PV triggers (RF 3, CB 2). The localization of non-PV foci were the superior vena cava (RF 3, CB 2), interatrial septum (RF2, CB 0), right atrium (RF 1, CB 0), left atrium (RF 1, CB 2) and unmappable (RF 0, CB 1).

Discussion

The present study successfully elucidated the recurrence of atrial arrhythmias after a PVI procedure. The main findings of our study are -1. an equal chance of ER (23%) with either ablation technique, RF and CB; 2. ER and RF-ablation are strong predictors for LR; 3. About 50% of the patients having an ER in the RF group experienced recurrence soon after the blanking period.

It is well known that a significant proportion of patients experience ER of atrial tachyarrhythmias during the first three months after ablation (9, 27). Those with symptomatic

Table 2. Perioperative Major Adverse Events during Follow Up.

	All	RF group	CB group	p value
Death related to the procedure	0	0	0	NA
Atrial-esophageal fistula	0	0	0	NA
Stroke	0	0	0	NA
Pericardial tamponade	1	1	0	1.00
Severe PV stenosis	1	0	1	0.48
Puncture site complication	4	1	3	0.36
Phrenic nerve palsy (transient)	1	0	1	0.48
Phrenic nerve palsy (permanent)	0	0	0	NA
Total	7	2	5	0.27

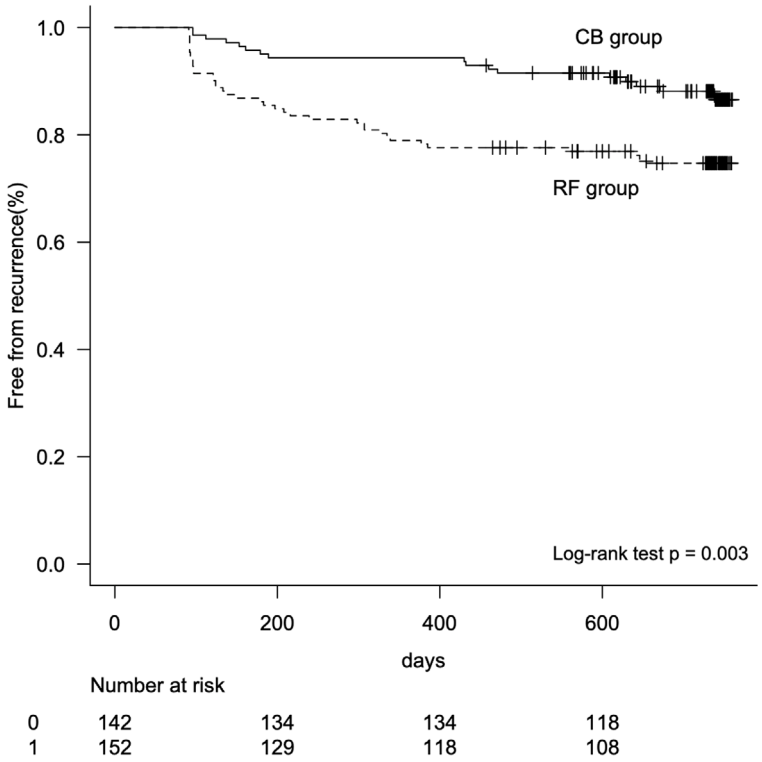

Figure 1. Kaplan-Meier curves showing freedom from late recurrence after the 3-month blanking period in the two groups. All patients were included in this analysis.

AF will develop the common clinical manifestations of AF irrespective of the timing of recurrence, with a pertinent risk of stroke. According to the expert consensus statements of 2007, 2012, and 2017 on catheter and surgical ablation of AF, the first three months after a PVI procedure are proposed as the blanking or stabilization period, and patients with recurring atrial tachyarrhythmia during this period should be treated with antiarrhythmic drugs instead of repeat ablation (2). The rationale for a blanking period during the follow-up after PVI is based on the assumption that either the incidence of AF decreases or is completely cured after that period (8, 9, 11). Although the mechanisms underlying an ER are still not fully understood, inflammatory responses to myocardial injury (14, 17), delayed scar maturation (15), and an alteration in the cardiac autonomic function (16) are the proposed causes for transiently induced atrial arrhythmias. While the mode of myocardial injury at the ablation site differs with the type of ablation device used (28, 29), and the degree of inflammation is also expected to differ (29), a uniform 3-month blanking period is still recommended for any ablation device (2, 3).

Recent studies have reported a significantly higher association of ER with LR with both RF (13, 19) and CB (20, 21) ablation. Interestingly, the frequency of ER in our study was similar (~23.5%) for both techniques. The subsequent LR in patients with ER, however, was significantly higher in the RF group compared to the CB group. This is in contrast to Vaishnav et al. who reported no difference in the recurrence rates between the two (22). The major difference between our study and theirs is that their study included 42-43% persistent patients, whereas ours were all paroxysmal. This may have affected the results. In addition, because this study was conducted before the publication of the CLOSE protocol (30) and effective AI values

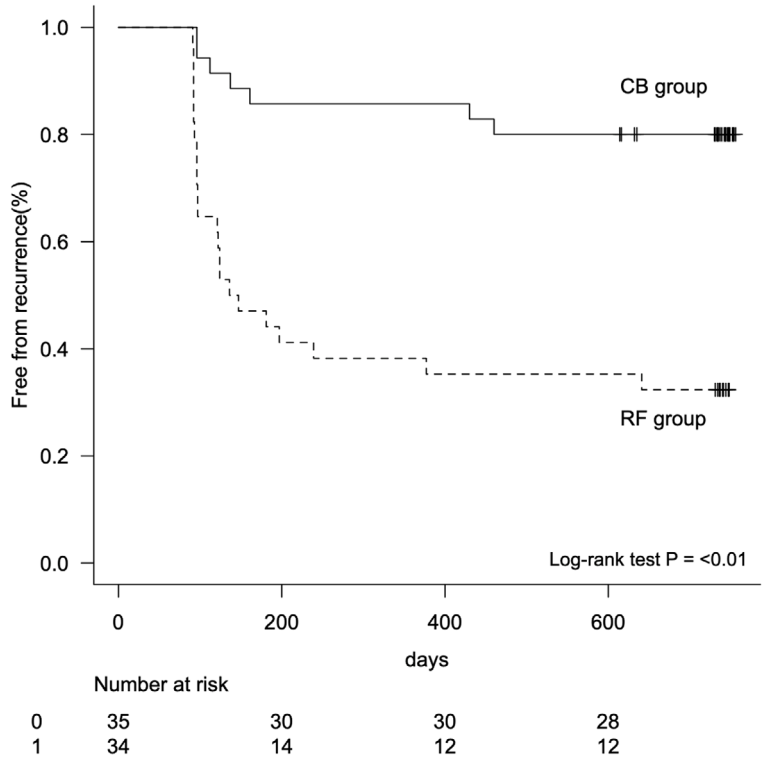

Figure 2. **Freedom from LR only in the patients with ER in both groups. The number of patients with ER was 34 in the RF group and 35 in the CB group.**

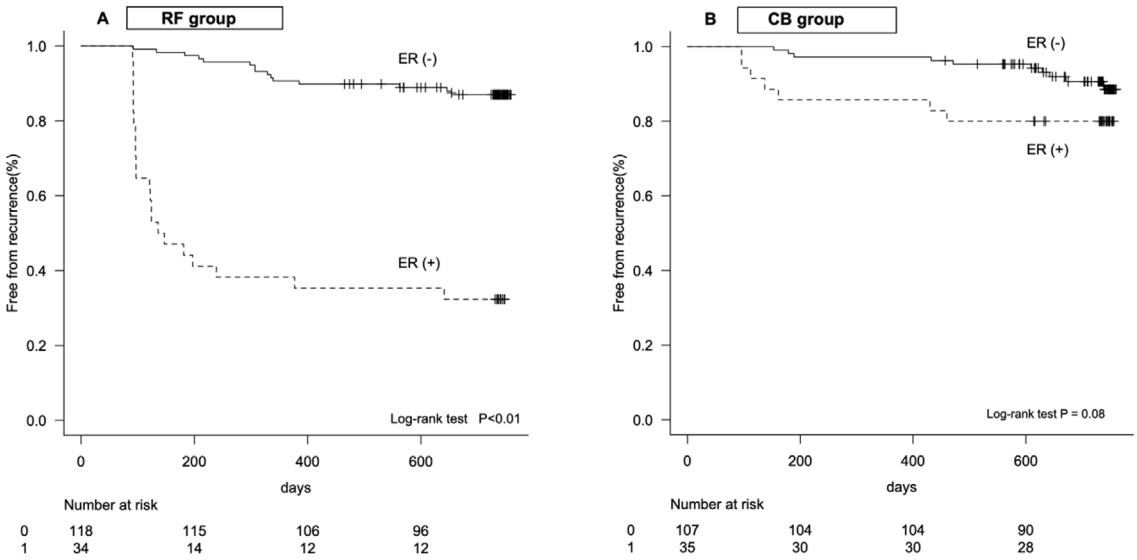

Figure 3. **Kaplan-Meier curves illustrating freedom from LR after the blanking period in the RF group (A) and in the CB group (B) with and without ER.**

had not yet been established, the AI we used is therefore lower than that described in other reports (30, 31), which may account for the high number of recurrences in the RF group. However, the initial isolation was achieved by keeping the adjacent ablation points within 4 mm of each other.

Half of the patients developing ER in the RF group relapsed within two months after the end of the blanking period. Patients who had a recurrence during the blanking periods were re-started with anti-arrhythmic drugs and discontinued at the end of the blanking period, which may have caused the recurrence immediately after the blanking period. Further, some patients had a recurrence in the last month of the blanking period and also continued to have episodes after the blanking period. These results were statistically significant for the RF group and suggest that the mechanisms for ER are different between RF and CB. Therefore, further research is required to elucidate the underlying mechanisms.

Our results also reveal that ER and RF-PVI are independent risk factors for LR, with a six-fold and three-fold increase in the likelihood of causing LR, respectively. Our

Table 3. Univariate and Multivariate Predictors of LR.

Variable	HR	95%CI	p
Univariate analysis			
Age	0.98	0.95-1.00	0.08
BMI	0.98	0.91-1.06	0.06
Hypertension	0.96	0.57-1.63	0.89
Diabetes	0.59	0.23-1.48	0.26
Coronary artery disease	0.70	0.25-1.94	0.49
Left atrium diameter	0.98	0.94-1.03	0.52
Early recurrence	5.25	3.08-8.94	<0.01
RF ablation	3.00	1.30-4.07	<0.01
Multivariate analysis			
Age	0.98	0.96-1.01	0.22
Early recurrence	6.12	3.56-10.51	<0.01
RF ablation	2.93	1.64-5.23	<0.01

CI: confidence interval, HR: hazard ratio

findings suggest that the management decisions regarding ER after PVI for AF may need to change depending on the ablation device used.

Because the trigger for AF may be something other than the PV (32-35), the cause of recurrence in patients who had a second ablation procedure was examined, but no difference was observed between the two groups.

Limitations

The current study focused on ER and differences between the 2 groups, however in this study, CB did better overall. There are multiple studies that have suggested the superiority of one technique over the other, however the available large, randomized trials support the fact that both energy sources are equivalent (3). It cannot be ruled out that the results of this study may have been influenced by some confounding factors (selection bias, center experience with RF and CB, differences in follow-up) that are inherent in retrospective studies. As mentioned in the text, the choice of the device was left to the operator. Although the operators were experienced in both CB and RF, the RF group was not a homogenous group, as there was a mix of patients undergoing PVI performed with FTI or AI. A 24-hour electrocardiogram was used to detect AF episodes during follow-up, rather than a more extended recordable device. Therefore, the detection of asymptomatic AF is limited. However, efforts were made to detect asymptomatic AF as early as possible by educating the patient to record the daily blood pressure and pulse measurements. This study retrospectively examined the effects of PVI performed at a single center. However, the follow-up method was the same for both study groups (RF and CB). Consequently, even for the ER and LR detection, bias due to differences in the follow-up methods between facilities was eliminated.

Table 4. Types of Recurrent Arrhythmias.

	RF		CB	
	ER	LR	ER	LR
AF	30 (2)	32 (4)	31 (3)	13 (2)
AFL	2 (2)	4 (2)	1 (1)	3 (1)
AT	1 (0)	1 (0)	3 (0)	1 (0)
PAC with short-run pattern	1 (0)	1 (0)	0	0

Values are presented as n (n of persistent arrhythmia).

Conclusion

It can be concluded that ER is a robust independent predictor of LR and the early recurrence of atrial arrhythmias during the blanking period after RF ablation for the PVI procedure significantly increases the chances of LR when compared to CB ablation.

The authors state that they have no Conflict of Interest (COI).

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