

Clinical Significance of Additional Ablation of Atrial Premature Beats after Catheter Ablation for Atrial Fibrillation

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Purpose: The clinical significance of post-procedural atrial premature beats immediately after catheter ablation for atrial fibrillation (AF) has not been clearly determined. We hypothesized that the provocation of immediate recurrence of atrial premature beats (IRAPB) and additional ablation improves the clinical outcome of AF ablation.

Materials and Methods: We enrolled 200 patients with AF (76.5% males; 57.4±11.1 years old; 64.3% paroxysmal AF) who underwent catheter ablation. Post-procedure IRAPB was defined as frequent atrial premature beats (≥6/min) under isoproterenol infusion (5 µg/min), monitored for 10 min after internal cardioversion, and we ablated mappable IRAPBs. Post-procedural IRAPB provocations were conducted in 100 patients. We compared the patients who showed IRAPB with those who did not. We also compared the IRAPB provocation group with 100 age-, sex-, and AF-type-matched patients who completed ablation without provocation (No-Test group).

Results: 1) Among the post-procedural IRAPB provocation group, 33% showed IRAPB and required additional ablation with a longer procedure time ($p=0.001$) than those without IRAPB, without increasing the complication rate. 2) During 18.0±6.6 months of follow-up, the patients who showed IRAPB had a worse clinical recurrence rate than those who did not (27.3% vs. 9.0%; $p=0.016$), in spite of additional IRAPB ablation. 3) However, the clinical recurrence rate was significantly lower in the IRAPB provocation group (15.0%) than in the No-Test group (28.0%; $p=0.025$) without lengthening of the procedure time or raising complication rate.

Conclusion: The presence of post-procedural IRAPB was associated with a higher recurrence rate after AF ablation. However, IRAPB provocation and additional ablation might facilitate a better clinical outcome. A further prospective randomized study is warranted.

Key Words: Atrial fibrillation, catheter ablation, atrial premature beats, recurrence

INTRODUCTION

Although radiofrequency catheter ablation (RFCA) for atrial fi-

brillation (AF) is an effective strategy for rhythm control, there remains a substantial recurrence rate.¹⁻³ The majority of AF cases are triggered in patients with paroxysmal AF (PAF) derived from pulmonary veins (PVs), although 10-30% of PAF patients and the majority of patients with persistent AF (PeAF) have non-PV triggers.^{1,4-6} Therefore, post-procedural detection and elimination of non-PV triggers might result in a better clinical outcome. Testing for immediate recurrence of AF after cardioversion is the common method for the detection of AF triggers.^{7,8} However, a post-procedural test for immediate recurrence of AF requires time, isoproterenol infusion,⁶ sedation, and electrical cardioversion. Moreover, repetitive electrical cardioversion may increase the risk of peri-procedural stroke in high-risk patients.⁹ Therefore, the clinical value of a post-proce-

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dural test for immediate recurrence of AF and additional ablation targeting remaining non-PV foci has not been clearly determined. With the development of a three-dimensional (3D)-electroanatomical software mapping system, the mapping and ablation of frequent atrial premature beats (APBs) has become relatively fast and accurate. Therefore, we hypothesized that non-PV-origin APBs may contribute to AF recurrence after catheter ablation. We defined the provocation of immediate recurrence of APBs (IRAPBs) as the detection of post-procedural frequent APBs (≥ 6 beats per minute) after electrical cardioversion under isoproterenol infusion ($5 \mu\text{g}/\text{min}$). The purposes of this study were to explore whether post-procedural IRAPB provocation and additional ablation for mappable frequent APBs affect the clinical outcome of AF ablation and whether IRAPB provocation lengthens procedure time or increases the complication rate. We also tested whether the type of induced tachyarrhythmias [AF or atrial tachycardia (AT)] and the presence of IRAPB are risk factors for clinical recurrence of AF after catheter ablation.

MATERIALS AND METHODS

Study population

The study protocol adhered to the Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei University Health System. All patients provided written informed consent. This study was a single-center retrospective comparison study, and patients were matched 1:1 by age, sex, and AF type. The study included patients with AF (76.5% males;

57.4 \pm 11.1 years old) who underwent RFCA between March 2011 and December 2012. The exclusion criteria were as follows: 1) permanent AF refractory to electrical cardioversion; 2) AF with valvular disease ($>$ grade II); 3) associated structural heart disease other than left ventricular hypertrophy; and 4) prior AF ablation. IRAPB provocation tests were conducted in 100 consecutive patients, who were compared with 100 age-, sex-, and AF-type-matched patients who completed ablation without any induction or mapping test (No-Test group) (Fig. 1). Among them, 67.0% of patients had PAF, and 33.0% had PeAF. 3D spiral computerized tomography (CT) scans (64 Channel, Light Speed Volume CT, Philips, Brilliance 63, the Netherlands) were performed to visually define atrial and PV anatomy in all patients. The presence of a left atrial (LA) thrombus was excluded by trans-esophageal echocardiography. All antiarrhythmic drugs were discontinued for a period corresponding to at least five half-lives. In total, 58 patients (29.0%) were taking amiodarone, which was discontinued for at least 4 weeks prior to the procedure. Anticoagulation therapy was maintained before catheter ablation.

Electrophysiologic mapping and radiofrequency catheter ablation

Intracardiac electrograms were recorded using the Prucka Cardio LabTM electrophysiology system (General Electric Health Care System Inc., Milwaukee, WI, USA), and catheter ablation was performed in all patients using 3D electroanatomical mapping (St. Jude Medical Inc., Minnetonka, MN, USA) merged with 3D spiral CT. We used an open irrigated-tip catheter (Celsius, Johnson & Johnson Inc., Diamond Bar, CA, USA; Coolflex,

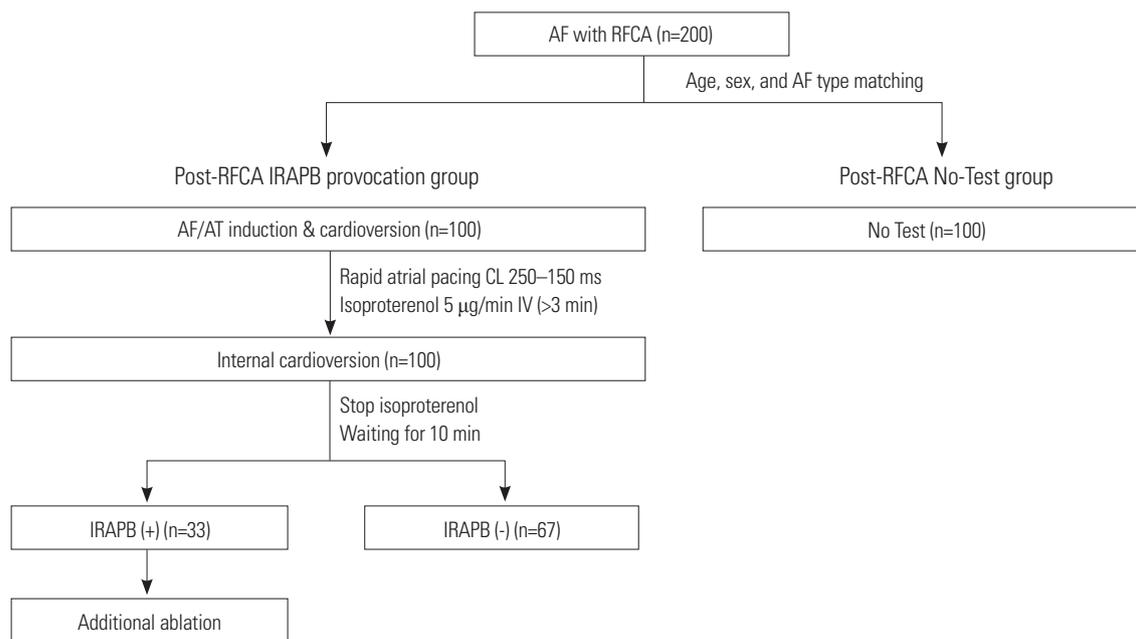


Fig. 1. Diagram of study protocol. We compared the clinical efficacy of post-procedural provocation for immediate recurrence of atrial premature beats (IRAPBs) under isoproterenol and additional ablation targeting these APBs ($n=100$) with 100 age-, sex-, and AF-type-matched patients who completed the procedure without an induction test (No-Test group). CL, cycle length; RFCA, radiofrequency catheter ablation; AF, atrial fibrillation; AT, atrial tachycardia.

ka, MN, USA) in the coronary sinus (CS) (Fig. 2B). After successful electrical cardioversion, we stopped isoproterenol infusion and waited for 10 minutes to map IRAPBs or immediate recurrence of AF originating from the non-PV foci (Fig. 2C). All mappable IRAPBs ($\geq 6/\text{min}$) or APBs triggering AF were mapped and ablated during the waiting period in the IRAPB provocation group. If AF recurred immediately (8 of 100) or during the mapping of IRAPBs (5 of 100) after cardioversion, we repeated internal cardioversion and attempted to ablate all mappable frequent IRAPBs.

Post-ablation follow-up

Patients were discharged without any anti-arrhythmic drugs and asked to visit the outpatient clinic at 1, 3, 6, and 12 months after RFCA and every 6 months thereafter for follow-up. Electrocardiography (ECG) was performed at each visit or anytime the patient reported palpitations. A Holter ECG (24-hour or 48-hour) and/or event recorder was evaluated at 3, 6, and 12 months after RFCA and every 6 months thereafter for at least 2 years, according to the 2012 HRS/EHRA/ECAS Expert Consensus Statement guidelines.¹² We defined recurrence of AF as any episode of AF or AT with a duration of at least 30 sec.¹³ If any ECG documented an AF episode within the 3-month blanking period during follow-up, the patient was diagnosed with an early recurrence. Any AF recurrence thereafter was diagnosed as clinical recurrence,¹³ and antiarrhythmic medications were

prescribed.

Data analyses

We compared clinical and electroanatomical markers in patients who experienced recurrence of AF with those in patients who remained in sinus rhythm. Data are expressed as mean \pm standard deviation. Statistical significance of the comparisons was assessed using Student's t-test, Fisher's exact test, and Kaplan-Meier analysis. A *p*-value of <0.05 was considered statistically significant.

RESULTS

Mapping and ablation of post-procedural IRAPBs

Fig. 1 summarizes the study protocol. Among the 100 patients in the IRAPB provocation group (70 PAF, 30 PeAF), we mapped and ablated IRAPBs in 33 patients, and 67 did not show post-procedural IRAPB after stopping the isoproterenol infusion (Table 1). The patients who tested positive for IRAPB had a higher CHADS₂ score ($p=0.003$), higher prevalence of previous stroke/transient ischemic attack ($p=0.002$), higher frequency of sinus node dysfunction ($p=0.025$), and a larger left atrial volume index (LAVI; $p<0.001$) than those who did not. Fig. 3A shows the 44 sites for IRAPBs and additional ablation in 33 patients with positive IRAPB, with locations as follows: superior vena cava

Table 1. Characteristics of IRAPB Provocation Group Depending on the Presence of IRAPBs and Additional Ablation

Variables	IRAPB (+) (n=33)	IRAPB (-) (n=67)	<i>p</i> value
Male, n (%)	22 (66.7)	54 (80.6)	0.128
Patient age (yrs)	57.6 \pm 9.5	56.6 \pm 11.7	0.692
PAF, n (%)	20 (60.6)	50 (74.6)	0.153
BMI (kg/m ²)	25.0 \pm 3.0	24.1 \pm 2.6	0.183
CHADS ₂ score, n (%)	1.1 \pm 1.1	0.6 \pm 0.8	0.003
Congestive heart failure	0 (0.0)	2 (3.0)	0.321
Hypertension	17 (51.5)	26 (38.8)	0.232
Age \geq 75 yrs	1 (3.0)	1 (1.5)	0.610
Diabetes	6 (18.2)	5 (7.5)	0.109
Stroke/TIA	7 (21.2)	2 (3.0)	0.002
Sinus node dysfunction, n (%)	5 (15.2)	2 (3.0)	0.025
LA diameter (mm)	41.1 \pm 4.1	39.1 \pm 4.8	0.052
LA volume index (mL/m ²)	36.2 \pm 11.2	28.2 \pm 8.5	<0.001
LV EF (%)	64.5 \pm 6.0	64.1 \pm 8.1	0.806
E/Em	9.7 \pm 3.6	8.9 \pm 3.0	0.278
Procedure time (min)	201.0 \pm 34.8	174.3 \pm 30.7	0.001
Ablation time (sec)	5280.0 \pm 1470.9	4617.0 \pm 1304.4	0.038
Procedure-related complications, n (%)	1 (3.0)	3 (4.5)	0.732
Follow-up duration (months)	17.4 \pm 5.7	18.1 \pm 7.4	0.643
Early recurrence rates (%)	36.4	10.4	0.002
Clinical Recurrence rates (%)	27.3	9.0	0.016

BMI, body mass index; E/Em, ratio of early mitral inflow peak velocity and Doppler-derived early diastolic mitral annular velocity; IRAPB, immediate recurrence of atrial premature beats after cardioversion; LA, left atrium; LV EF, left ventricular ejection fraction; PAF, paroxysmal atrial fibrillation; TIA, transient ischemic attack.

(n=12), interatrial septum (n=11), CS ostium (n=10), ligament of Marshall (n=6), crista terminalis (n=3), and LA posterior wall (n=2, one PAF and one PeAF). The RA volume index of the patients with RA-origin IRAPB ($21.1 \pm 5.6 \text{ mL/m}^2$) tended to be greater than those with LA origin IRAPB ($19.5 \pm 4.6 \text{ mL/m}^2$) without statistical significance ($p=0.462$). In patients with frequent and uni-focal IRAPBs, 3D-electroanatomical mapping was utilized for accurate mapping of non-PV foci or recovered conduction at linear ablation sites (Fig. 3B). The patients who underwent IRAPB ablation required a significantly longer procedure time ($p=0.001$) and ablation time ($p=0.038$) than those without IRAPB (Table 1). However, additional ablation for IRAPBs did

not increase the procedure-related complication rate ($p=0.732$).

Presence of post-procedural IRAPBs is associated with higher clinical recurrence rate

During 18.0 ± 6.6 months of follow-up, the early recurrence rate and clinical recurrence rate were 19% and 15%, respectively, for the IRAPB-provocation group. Among 51 patients with positive post-procedural inducibility before isoproterenol infusion, there was no significant difference in recurrence rates with respect to the type of induced atrial tachyarrhythmias (AF vs. AT; $p=0.694$) (Table 2). However, the patients with positive IRAPB showed a significantly higher early recurrence rate (36.4% vs.

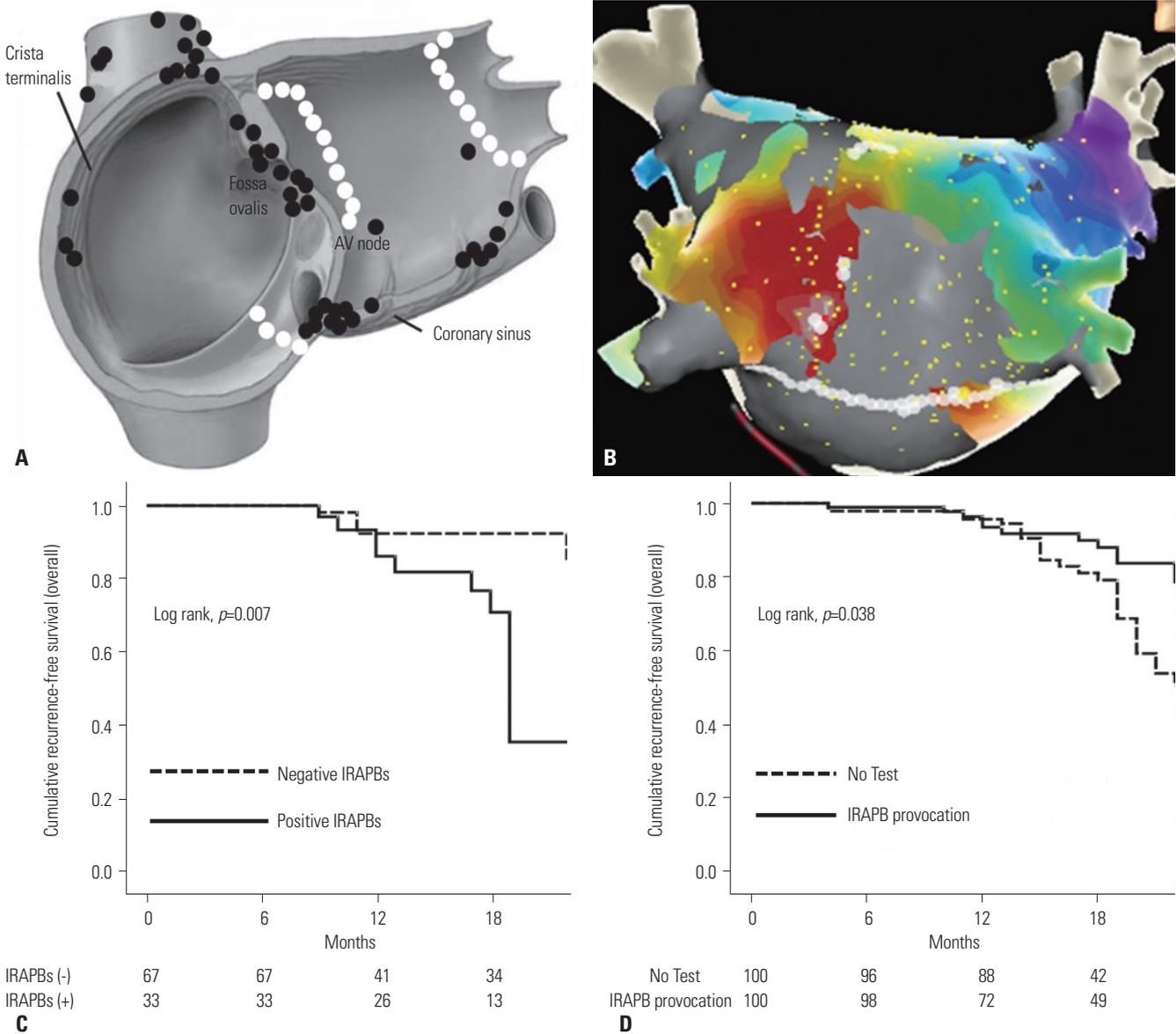


Fig. 3. (A) Locations of post-procedural IRAPBs and additional ablation sites (black circles). White circles indicate the standard ablation sites for PAF. (B) Mapping and ablation of post-procedural IRAPB utilizing 3D activation map. Quick activation mapping by multipolar catheter revealed non-PV foci located on LA posterior wall (white dots) and conduction gap at posterior inferior linear ablation site. We eliminated IRAPBs and ablation gap on posterior inferior line concomitantly. (C) Kaplan-Meier curve for AF-free survival comparing patients with post-procedural IRAPBs to those without IRAPBs. (D) Kaplan-Meier graph of AF-free survival comparing the IRAPB provocation group to the No-Test group. IRAPBs, immediate recurrence of atrial premature beats; 3D, three-dimensional; PV, pulmonary vein; LA, left atrial; AF, atrial fibrillation; PAF, paroxysmal AF.

10.4%; $p=0.002$) and clinical recurrence rate (27.3% vs. 9.0%; $p=0.016$) than those with negative IRAPBs, despite additional ablation and a longer procedure time ($p=0.001$) (Table 1). On multivariate logistic regression analysis, IRAPB ($\beta=1.398$; odds ratio=4.046; 95% confidence interval 1.14–14.39; $p=0.031$) was independently associated with clinical recurrence after RFCA of AF (Table 3). Table 3 also shows that the type of induced atrial tachyarrhythmias, AT ($p=0.308$) or AF ($p=0.422$), was not associated with clinical recurrence. Kaplan-Meier analysis showed consistently worse clinical outcome in patients with positive IRAPBs after the procedure (log rank, $p=0.007$) (Fig. 3C).

IRAPB provocation and ablation results in better clinical outcome of AF ablation

We compared patient characteristics, procedure time, procedure-related complication rate, and clinical outcome between the patients with IRAPB provocation and age-, sex-, and AF-type-matched patients who completed the procedure without an induction test (No-Test group) (Table 4). The baseline characteristics, LA diameter ($p=0.187$), LAVI ($p=0.105$), procedure times ($p=0.540$), ablation times ($p=0.848$), and procedure-related complication rates ($p=0.702$), were not significantly different between the two groups. However, the clinical recurrence rate (15.0% vs. 28.0%; $p=0.025$) was significantly lower in the IRAPB provocation and ablation group than in the No-Test group. Kaplan-Meier AF-free survival analysis indicated a consistently better clinical outcome in the IRAPB provocation group than in the No-Test group (log rank, $p=0.038$) (Fig. 3D).

DISCUSSION

In the current study, we reported the potential usefulness of post-procedural IRAPB provocation and additional ablation during AF catheter ablation. The patients who showed post-procedural IRAPB under isoproterenol had a clearly higher clinical recurrence rate of AF than those without IRAPB. However, clinical outcome was better in patients with routine post-procedural IRAPB provocation and additional ablation than in those who completed the procedure without an induction test. This study revealed the importance of remaining non-PV foci as a mechanism of recurrence after AF catheter ablation. Therefore, a further prospective study with a larger number of patients is warranted to prove whether routine IRAPB provocation facilitates an improved clinical outcome of AF catheter ablation.

Role of post-procedural detection of AF triggers or substrate

AF is generally a progressive disease, and the mechanism for generation of AF is not yet fully understood.^{1,14} Coumel^{15,16} suggested that trigger factors or trigger foci initiate AF, and arrhythmic substrate leads to its persistence. In this study, we explored the clinical significance of post-procedural tests for AF triggers or IRAPB. It is known that 70–90% of AF triggers exist around PVs in patients with PAF; however, non-PV foci are more common in those with PeAF.⁴⁻⁶ Generally, PV isolation at the level of the PV antrum is a cornerstone of catheter ablation for AF.¹⁷⁻¹⁹ In this study, by isolating PVs during the procedure, all post-

Table 2. Clinical Outcomes Depending on the Type of Post-Procedural Atrial Tachyarrhythmias (AT/AF) Induced by High-Current Rapid Atrial Pacing

Variables	AT induction (n=35)	AF induction (n=16)	p value
Follow-up duration (month)	18.2±6.1	17.3±4.9	0.625
Early recurrence rates (%)	28.6	31.3	0.849
Clinical recurrence rates (%)	20.0	25.0	0.694

AF, atrial fibrillation; AT, atrial tachycardia.

Table 3. Factors Associated with Clinical Recurrence after Radiofrequency Catheter Ablation (Logistic Regression Analyses)

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	p value	OR	95% CI	p value
PAF	0.590	0.19–1.84	0.363	0.986	0.26–3.74	0.983
Male	1.312	0.34–5.10	0.695	1.373	0.29–6.56	0.691
Age (yrs)	1.014	0.96–1.07	0.596	1.001	0.94–1.07	0.967
Diabetes	4.052	1.02–16.13	0.047	3.205	0.71–14.41	0.129
Pre-RFCA LA volume index (mL/m ²)	1.046	0.99–1.11	0.132			
Pre-RFCA LV EF (%)	1.044	0.96–1.13	0.304	1.018	0.93–1.12	0.711
Pre-RFCA E/Em	1.009	0.85–1.21	0.919	0.983	0.79–1.22	0.878
AT or AF induction (+)	3.094	0.91–10.49	0.070			
AT induction (+)	1.781	0.59–5.41	0.308			
AF induction (+)	1.625	0.50–5.31	0.422			
IRAPB (+)	3.812	1.22–11.87	0.021	4.046	1.14–14.39	0.031

AF, atrial fibrillation; AT, atrial tachycardia; CI, confidence interval; E/Em, ratio of early mitral inflow peak velocity and Doppler-derived early diastolic mitral annular velocity; IRAPB, immediate recurrence of atrial premature beats; LA, left atrial; LV EF, left ventricular ejection fraction; OR, odds ratio; PAF, paroxysmal atrial fibrillation; RFCA, radiofrequency catheter ablation.

procedural IRAPBs arose from non-PV foci. Although the presence of IRAPBs from these non-PV foci clearly worsened the clinical outcome of AF ablation, additional ablation targeting IRAPB might result in a lower recurrence rate than that of the No-Test group. Therefore, remaining non-PV-origin IRAPB may play an important role in the recurrence mechanism of AF in the No-Test group.

Clinical significance of non-PV foci

APBs that trigger AF frequently arise from PVs,²⁰ and cardiac autonomic nerves mainly connect to the heart along the PV antral area.^{4,21,22} Therefore, bi-antral PV isolation is effective for the elimination of PV triggers,^{23,24} cardiac autonomic denervation,²⁵ and substrate modification. However, PV isolation may not be sufficient to control AF due to the presence of non-PV foci or atrial substrate remodeling, particularly in patients with PeAF.^{26,27}

Clinically, complex fractionated atrial electrograms (CFAEs) are known to play a role in maintaining AF^{28,29} and act as a target for AF catheter ablation.^{29,30} Verma, et al.³¹ considered CFAE ablation to be a non-PV substrate and a trigger of ablation, and Lemery, et al.³² co-localized the area of CFAE and cardiac autonomic ganglionated plexi by nerve stimulation. However, CFAE includes both the active driver of AF and passive wave breakers, and CFAE-guided AF ablation carries the risk of unnecessary cardiac tissue damage. In this study, we ablated non-PV foci targeting post-cardioversion IRAPBs and demonstrated a better clinical outcome.

Mapping and ablation technique for non-PV foci

We previously reported that an excessively long ablation duration for substrate modification results in a poor clinical outcome.^{33,34} Therefore, limited and sophisticated ablation for non-

Table 4. Characteristics Comparing IRAPB Provocation/Ablation Group vs. No-Test Group

Variables	All (n=200)	Provocation of IRAPB (n=100)	No test (n=100)	p value
Male, n (%)	153 (76.5)	76 (76.0)	77 (77.0)	0.868
Age (yrs)	57.4±11.1	57.0±11.0	57.9±11.2	0.551
PAF, n (%)	134 (67.0)	70 (70.0)	64 (64.0)	0.369
BMI (kg/m ²)	24.9±3.9	24.5±2.8	25.3±4.7	0.233
CHADS ₂ score, n (%)	0.8±1.0	0.8±0.9	0.9±1.0	0.309
Congestive heart failure	6 (3.0)	2 (2.0)	4 (4.0)	0.410
Hypertension	92 (46.0)	43 (43.0)	49 (49.0)	0.397
Age ≥75 yrs	4 (2.0)	2 (2.0)	2 (2.0)	1.000
Diabetes	28 (14.0)	11 (11.0)	17 (17.0)	0.223
Stroke/TIA	18 (9.0)	9 (9.0)	9 (9.0)	1.000
Sinus node dysfunction, n (%)	10 (5.0)	7 (7.0)	3 (3.0)	0.196
LA diameter (mm)	40.2±4.8	39.8±4.6	40.7±5.0	0.187
LA volume index (mL/m ²)	32.0±10.2	30.8±10.1	33.2±10.2	0.105
LV EF (%)	63.6±7.7	64.2±7.5	63.0±7.9	0.275
E/Em	9.7±4.3	9.2±3.2	10.2±5.1	0.107
RFCA procedural parameters				
Procedure time (min)	180.9±34.5	182.5±34.2	179.4±34.8	0.540
Ablation time (sec)	4803.5±1286.4	4822.8±1384.4	4786.4±1199.7	0.848
Ablation strategy, n (BDB rate, %)				
PVI	200 (100.0)	100 (100.0)	100 (100.0)	>0.999
CTI block	192 (100.0)	94 (100.0)	98 (100.0)	0.155
Roof line	66 (97.0)	30 (100.0)	36 (94.4)	0.369
Posterior-inferior line	51 (71.9)	29 (66.7)	22 (76.5)	0.258
Anterior linear line	53 (67.9)	26 (57.1)	27 (78.6)	0.873
Procedure-related complications, n (%)				
Hemopericardium	4 (2.0)	1 (1.0)	3 (3.0)	0.315
Mild PV stenosis	1 (0.5)	1 (1.0)	0 (0.0)	0.319
Groin hematoma	2 (1.0)	2 (2.0)	0 (0.0)	0.157
Follow-up duration (months)	18.0±6.6	17.9±6.9	18.2±6.4	0.694
Early recurrence rates (%)	30.5	19.0	42.0	<0.001
Clinical recurrence rates (%)	21.5	15.0	28.0	0.025

BMI, body mass index; E/Em, ratio of early mitral inflow peak velocity and Doppler-derived early diastolic mitral annular velocity; IRAPB, immediate recurrence of atrial premature beats after cardioversion; LA, left atrium; LV EF, left ventricular ejection fraction; PAF, paroxysmal atrial fibrillation; PV, pulmonary vein; PVI, pulmonary vein isolation; TIA, transient ischemic attack; BDB, bidirectional block; RFCA, radiofrequency catheter ablation; CTI, cavotricuspid isthmus.

PV foci based on post-procedural IRAPB might be beneficial for a better clinical outcome. However, detection and ablation of non-PV foci are not simple. We targeted non-PV foci immediately after cardioversion under isoproterenol (5 µg/min) infusion. As we adhered to the linear ablation strategy, including the anterior line¹⁰ in patients with PeAF, re-initiation of AF was uncommon (8%) after cardioversion and cessation of isoproterenol infusion, and most non-PV foci remained as frequent APBs. We were able to map those non-PV IRAPBs based on the areas defined by linear ablation lines.¹¹ Quick and limited 3D activation mapping utilizing a multi-electrode catheter was useful for accurate mapping and limited ablation of frequent non-PV-origin APBs in certain patients. We mapped and ablated IRAPBs during the isoproterenol cooling-down period until no APBs appeared.

Limitations

The patients included in this study were a highly selective group referred for RFCA, and the number of patients was limited. As this was a retrospective single-center study, there might have been a selection bias, despite comparing two groups matched for age, sex, and AF type. Considering that most IRAPBs were mapped and ablated within 10 minutes after stopping isoproterenol infusion, infrequent IRAPBs, multi-focal APBs, and catecholamine-insensitive APBs may not have been eliminated in this study protocol. In addition, we did not challenge isoproterenol again after IRAPB ablation.

Conclusion

The patients who showed post-procedural IRAPB under isoproterenol had a clearly higher clinical recurrence rate of AF. However, careful mapping and ablation for post-procedural IRAPB safely resulted in a better clinical outcome without requiring a longer procedure time compared to those who completed the procedure without an induction test. Therefore, a future prospective study with a larger number of patients is warranted to determine whether routine IRAPB provocation facilitates an improved clinical outcome of AF catheter ablation.

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