Atrial late potentials are associated with atrial fibrillation recurrence after catheter ablation

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Abstract

Introduction: Few non-invasive parameters have been identified for predicting atrial fibrillation (AF) recurrence after catheter ablation (CA). This study aimed to assess the association between AF recurrence and atrial late potentials (ALP) measured using P-wave signal-averaged electrocardiography (P-SAECG). **Methods and results:** Consecutive patients with paroxysmal AF who underwent first CA at our institution between August 2015 and August 2019 were enrolled. P-SAECG was performed before CA. Two ALP parameters were evaluated: root mean square voltage during the terminal 20 ms (RMS $_{20}$) and P-wave duration (PWD). Positive ALP was defined as an RMS $_{20}$ <2.2 μV and/or a PWD >115 ms. Patients were divided into the Recurrence and Non-recurrence groups based on AF recurrence at the 1-year follow-up after CA. Of 190 patients (age: 65±11 years, 37% women) enrolled in this study, 21 (11%) had AF recurrence. Positive ALP rate was significantly higher in the Recurrence group than in the Non-Recurrence group (86% vs. 64%, P=0.04) despite there being no differences in other baseline characteristics between the two groups. In the multivariate analysis, positive ALP was an independent predictor of AF recurrence (odds ratio: 3.83, 95% confidence interval: 1.05–14.1, P=0.04). **Conclusion:** Positive ALP on pre-CA P-SAECG was associated with AF recurrence after CA.

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Keywords: atrial fibrillation; atrial late potentials; catheter ablation; pulmonary vein isolation; recurrence

Introduction

Atrial fibrillation (AF), the most frequently encountered cardiac arrhythmia,[1] is associated with high mortality and morbidity, mainly due to thromboembolic complications and heart failure. In recent times, catheter ablation (CA) has been found to be effective for treating AF.[2,3] However, AF recurs after CA in 10–30% of patients,[4.5] and few reports have focused on the use of electrocardiography (ECG) for predicting AF recurrence after CA.

Signal-averaged electrocardiography (SAECG) is a technique used for recording microvolt-potentials from the body surface. QRS-SAECG is commonly performed, and positive QRS-SAECG findings have been found to be associated with fatal ventricular arrhythmias and sudden cardiac death.[6] In contrast, robust evidence on the use of P-wave SAECG (P-SAECG) is lacking. Previous reports have demonstrated that P-SAECG findings of atrial late potentials (ALP) could be indicative of atrial fibrosis, an arrhythmogenic substrate, in patients with AF. Therefore, P-SAECG could be useful for identifying patients at risk of developing new-onset AF[7,8] and those in whom conversion from paroxysmal to chronic AF is likely.[9]

We hypothesized that pre-recorded ALP would differ between patients with and without AF recurrence after CA, and positive ALP would be associated with AF recurrence.

Methods

Study population

This was a single-center, nonrandomized, observational study. Consecutive patients with paroxysmal AF who underwent CA between August 2015 and August 2019 at our institution were retrospectively evaluated. We excluded patients who 1) did not undergo P-SAECG, 2) were receiving a class I, III, or IV antiarrhythmic drug at the time of P-SAECG, or 3) were lost to follow-up (Figure 1). This study was approved by the Ethics Committee of Kitasato University Hospital (No. B18-197).

P-wave signal-averaged electrocardiography

P-SAECG with P-wave triggering was performed before CA using the FCP-8800 (Fukuda Denshi, Ltd, Tokyo, Japan) with 12 standard ECG leads. First, the skin at the electrode placement site was cleaned with alcohol and scrubbed with a rubbing pad because the signals were of relatively low amplitude. Subsequently, the signals from each lead were amplified and filtered between 40 Hz and 300 Hz. A modified X, Y, and Z lead system was used to trigger signal averaging from the P-wave. The signal was passed through a P-wave recognition program to eliminate atrial extrasystole, and a signal of 200 beats with an error vector magnitude of <0.4 μV was obtained. The following two ALP parameters were evaluated: root mean square

voltage during the terminal 20 ms (RMS_{20}) and filtered P-wave duration (PWD). RMS_{20} and PWD data were automatically calculated by the system. Positive ALP was defined as an RMS_{20}<2.2 μV and/or a PWD >115 ms. The standard value was based on an analysis of 120 healthy individuals.[10]

Assessment of baseline characteristics

Baseline characteristics such as age, sex, duration of AF history, body mass index, underlying diseases, and medications used were evaluated. Additionally, pre-CA 12-lead ECG parameters, echocardiographic parameters, and blood test findings were evaluated.

Ablation procedure

Radiofrequency catheter ablation (RFCA) or cryoballoon ablation (CBA) was performed at the discretion of the operators. CA was performed under general anesthesia with 0.4 μg/kg/h of dexmedetomidine, 0.1 mg/kg/h of propofol, and 0.5–1.0 mg of injected fentanyl with non-invasive or invasive positive airway pressure for respiratory support. Esophageal temperature monitoring (Esophastar®, Japan Lifeline Co., Ltd., Tokyo, Japan) was performed. Vascular access was obtained and 2000–3000 U of heparin was intravenously injected, followed by continuous infusion with a target activated clotting time of 300–350 s. A single transseptal puncture was performed using intracardiac echocardiography (SOUNDSTAR®, Biosense Webster, Inc., Diamond Bar, CA, USA or ViewFlex Xtra®, Abbott, St. Paul, MN, USA). For RFCA, two long sheaths (Agilis and 8.0 Fr SL-0 sheath; Abbott, St Paul, MN, USA) were inserted into the left atrium (LA). For CBA, a FlexCath Advance Steerable Sheath® (Medtronic, Inc., Minneapolis, USA) was inserted into the LA. A detailed 3D model of the LA was created using a high-density mapping catheter (PENTARAY®, Biosense Webster Inc., Diamond Bar, CA, USA; HD Grid Mapping Catheter Sensor Enabled®, Abbott, St. Paul, MN, USA; or IntellaMap Orion®, Boston Scientific, Inc, Washington DC, USA) and 3D mapping system (CARTO3®, Biosense Webster, Inc., Diamond Bar, CA, USA; EnSite Velocity, Abbott, St. Paul MN, USA; or Rhythmia HDx, Boston Scientific, Inc, Washington DC, USA). Extensive circumferential ablation of the ipsilateral pulmonary veins (PVs) was performed with irrigated-tip ablation catheters (THERMOCOOL SMARTTOUCH(r) SF, Biosense Webster, Inc., Diamond Bar, CA, USA; TactiCath, Abbott, St. Paul, MN, USA; or IntellaNav MiFi OI, Boston Scientific, Inc, Washington DC, USA) for RFCA. The radiofrequency energy was 30–35 W, and ablation was performed using ablation index, lesion size index, and local impedance drop as indicators of effective lesion formation. Additional procedures such as posterior wall or superior vena cava isolation were performed at the operators' discretion. At least 15 min of observation was performed after pulmonary vein isolation (PVI), and spontaneous reconnection and dormant conduction were evaluated by administering 2–4 μg of isoproterenol followed by rapid injection of 20 mg adenosine triphosphate to find the electrical gaps. Additional RFCA was performed at gap areas adjacent to the first-pass ablation line. For CBA, right-sided phrenic nerve pacing was performed to detect phrenic nerve injury. A cryoballoon catheter with a 28-mm balloon (Arctic Front Advance II®, Medtronic, Inc., Minneapolis, USA) and a PV mapping catheter (Achieve Mapping Catheter®, Medtronic, Inc., Minneapolis, USA) were inserted, and freezing for 3 min was performed on each PV. Additional freezing was performed if the PV was not isolated. After PVI, exit blocks were confirmed based on the pacing from the circular mapping catheter in each PV.

Follow-up

Patients were discharged 3±1 days after CA. After CA, we performed 12-lead ECG every 1 or 2 months and 24 h Holter recording at 6 and 12 months post-CA. We defined AF recurrence as any atrial tachyarrhythmia lasting [?]30 s detected on ECG after a 3-month blanking period during the 1-year observational period. Patients with AF recurrence were categorized into the Recurrence group, and those without AF recurrence were categorized into the Non-Recurrence group.

Statistical analysis

Continuous data are expressed as means +- standard deviations or as medians with interquartile ranges. Categorical data are presented as absolute values and percentages. Continuous variables were compared using the t-test or Mann–Whitney U test if applicable, and dichotomous variables were compared using the

chi-square test or Fisher's exact test. A *P*- value of <0.05 was considered statistically significant. Univariate and multivariate logistic regression analyses were performed to determine the clinical factors associated with AF recurrence. Parameters with *P* -values <0.20 were included in the multivariate logistic regression analysis performed to assess the independent predictors of AF recurrence. All analyses were performed using JMP 14 software (SAS Institute, Cary, NC, USA).

Results

Comparison of baseline characteristics

Complete bidirectional conduction block of all four PVs was achieved in all patients. Among the 190 patients enrolled, 21 (11%) experienced AF recurrence during the follow-up period. The clinical characteristics of the enrolled patients are shown in Table 1. There were no significant differences between the two groups in echocardiographic parameters, including LA dimension; 12-lead electrocardiographic parameters; underlying diseases; medications; $CHADS_2$ score; and CA procedure performed.

P-SAECG findings and AF recurrence

The P-SAECGs of representative patients are shown in Figure 2. The left and right panels show the P-SAECGs of one patient each from the Recurrence (RMS_{20}: 1.6 μV, PWD: 128 ms) and Non-Recurrence (RMS_{20}: 3.1 μV, PWD: 91 ms) groups, respectively. The representative patient from the Recurrence group met both the criteria for ALP positivity. Table 2 shows positive ALP rates of both groups. The rate of positive ALP was significantly higher in the Recurrence group than in the Non-Recurrence group (85.7% vs. 63.9%,P =0.04).

Predictors of AF recurrence

Sex, PVI alone, and positive ALP were included in the multivariate analysis because they had *P*- values <0.20 in the univariate analysis. In the multivariate analysis, positive ALP was an independent predictor of AF recurrence (odds ratio: 3.83, 95% confidence interval: 1.05–14.1, P =0.04, Table 3).

Discussion

This study showed that the rate of positive ALP before CA was significantly higher in the Recurrence group than in the Non-recurrence group despite there being no significant differences in baseline characteristics, including the LA dimensions. Furthermore, multivariate analysis showed that positive ALP was an independent factor associated with AF recurrence after CA.

P-SAECG and atrial remodeling

PWD is an electrophysiological parameter that reflects complete atrial conduction. Studies[11-13] have reported that P-SAECG findings are closely related to AF recurrence after CA. Okumura et al.[12] performed P-SAECG before and after CA (n=51) in patients with paroxysmal and persistent AF. Patients with successful CA had a more significant shortening of the PWD (from 146 ± 13 to 136 ± 12 ms; P ¡0.01) than those in whom recurrence occurred (from 167 +- 15 to 157 +- 15 ms; P= 0.18). Ogawa et al.[11]reported a significant reduction in PWD (from 161 +- 7 to 151 +- 8 ms; ΔPWD 10 ± 7 ms; P <0.0001) after CA in patients with paroxysmal and persistent AF (n=27), although they observed no significant shortening in PWD in patients with AF recurrence. Masuda et al.[13] performed P-SAECG before and 1 day after CA (n=88) in patients with paroxysmal AF. Although there were no differences in pre-CA P-SAECG findings, AF recurrence was significantly more common in patients with a long PWD and low RMS_{20} 1 day after CA than those without them (54% vs. 19%, P=0.001). These reports suggest that improvement in atrial conduction parameters could be associated with a reduced recurrence rate after CA because ALP is a marker of abnormal atrial electrical properties such as intra-atrial or inter-atrial conduction disturbance.

In our study, we evaluated a large number of patients with paroxysmal AF and focused on the prediction of AF recurrence based on positive ALP before CA. Consequently, the rate of positive ALP before CA (a long PWD and a low RMS_{20}) was significantly higher in the Recurrence group than in the Non-recurrence

group. These results suggest that the parameter of positive ALP on P-SAECG could be used to detect the electrical remodeling.

Prediction of AF recurrence after CA using P-SAECG

Structural and electrical remodeling have been reported as the causes of arrhythmias.[14] Findings suggestive of dilatation on non-invasive modalities such as echocardiography or computed tomography could indicate structural remodeling of the atrium. Preoperative left atrial diameter (LAD) has been reported to be associated with AF recurrence after CA.[15,16] Structural remodeling in the form of LA enlargement is the most common arrhythmogenic substrate. P-wave duration on surface 12-lead ECG has also been associated with AF recurrence after CA.[17,18] A long P-wave duration is associated with an enlarged LA[19] and atrial conduction disturbance.[20] We demonstrated that positive ALP was an independent predictor of AF recurrence after CA, and there were no significant differences in the LAD and P-wave duration on surface 12-lead ECG between the Recurrence and Non-Recurrence groups. This may be because our study population only consisted of patients with paroxysmal AF who had a short disease duration and in whom structural remodeling might not have progressed. ALP could reflect subtle changes in the atria that are not structural changes and do show up as changes in the P-wave on 12-lead ECG. Based on the results of our study, we speculate that ALP can reveal the progression of electrical remodeling in patients without structural remodeling.

Limitations

Several limitations of this study need to be acknowledged. First, this was a single-center retrospective study that included a limited number of patients, which resulted in the possibility of selection bias. Second, P-SAECG is sometimes difficult to perform because of irregular cardiac rhythms such as atrial or ventricular premature beats, environmental noise causing electrocardiogram interference, or overlap between the end of the P-wave and the beginning of the QRS complex. Third, asymptomatic recurrence during the follow-up period could not be fully identified; therefore, the recurrence rate may be underestimated. Fourth, the cause of AF recurrence, such as PV reconnection or other non-PV foci, could not be identified. Finally, P-SAECG can only be performed in patients with sinus rhythm; therefore, it might be challenging to apply our findings to patients with non-paroxysmal AF. Further prospective studies are needed to ascertain the relationship between AF recurrence and ALP.

Conclusion

Positive ALP on pre-CA P-SAECG was associated with AF recurrence after CA.

Disclosure

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Figure legends

Figure 1. Patient enrolment flow chart.

This figure shows the flowchart of enrolment of patients in this study. The enrolment procedure has been described in detail in the main text.

AF: atrial fibrillation, P-SAECG: P-wave signal-averaged electrocardiography.

Figure 2. Representative P-SAECG findings

P-SAECGs of representative patients are shown. Solid perpendicular lines indicate the start and end of the P-wave. Dotted perpendicular lines indicate the point preceding the end of the P-wave by 20 ms. Positive ALP was defined as an RMS_{20} <2.2 μV or a PWD >115 ms.

P-SAECG: P-wave signal-averaged electrocardiography, RMS_{20}: root mean square voltage during the terminal 20 ms, PWD: P-wave duration.

Figure 1. Patients enrolment flow chart

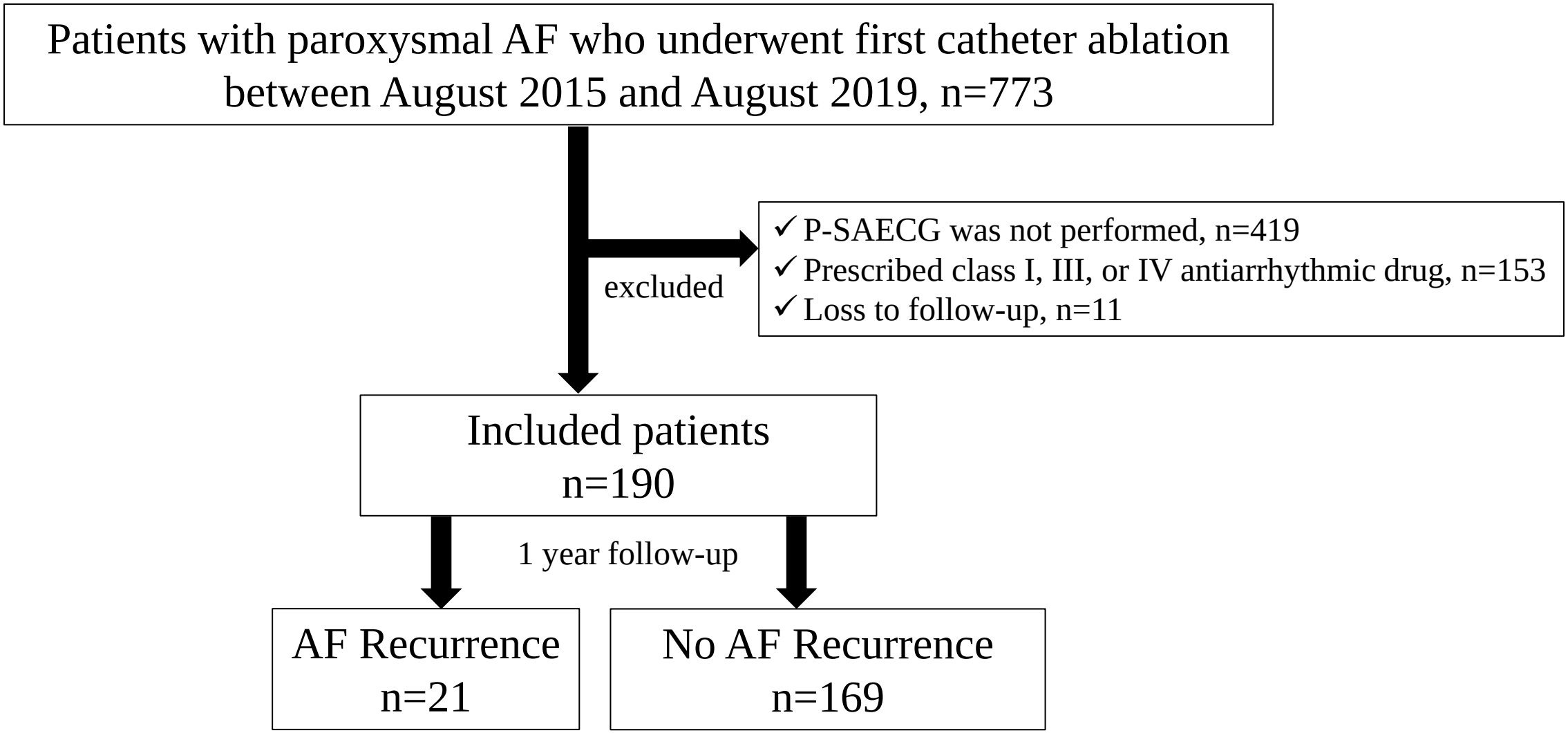
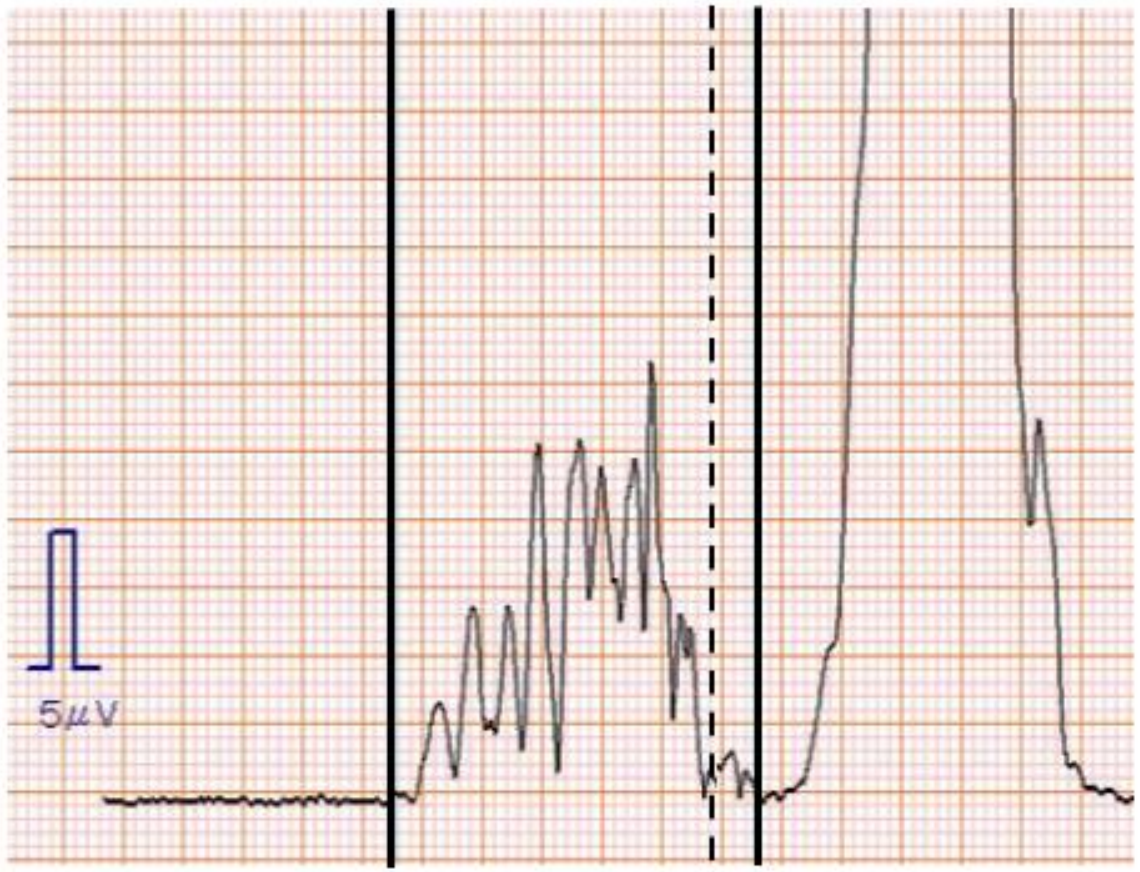


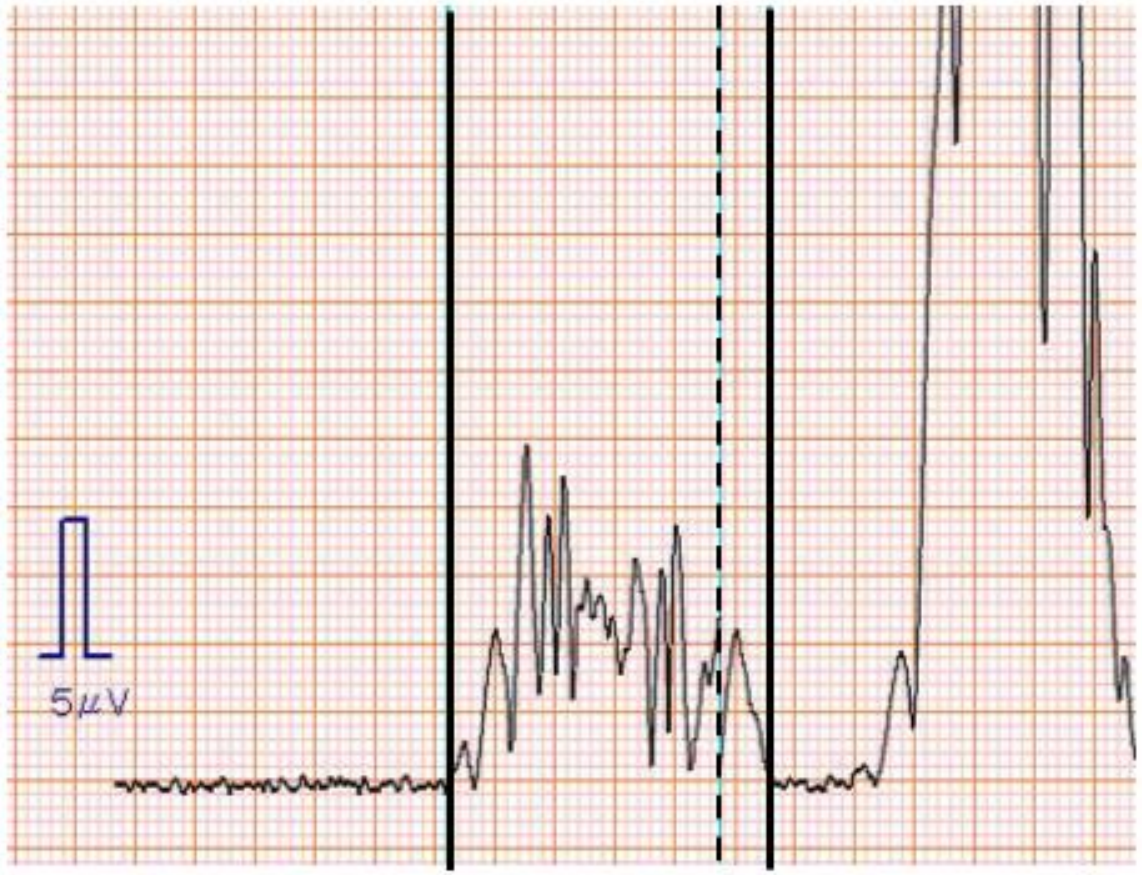
Figure 2. Representative P-SAECG findings

Recurrence



RMS_{20}:1.3 μV, PWD:125 ms

Non-Recurrence



RMS_{20}:3.2 μV, PWD:112 ms

Table1. Comparison of baseline characteristics between patients with and without recurrence

	Total n = 190	Recurrence group n = 21	Non-Recurrence group n = 169	*P*-value
Age (years)	65 ± 11	67 ± 12	65 ± 11	0.38
Female, n (%)	71 (37.4)	11 (52.4)	60 (35.5)	0.13
BMI (kg/m^2)	23.8 ± 3.5	24.4 ± 3.7	23.8 ± 3.5	0.43
Echocardiographic parameters				
LAD (mm)	37.7 ± 5.3	38.1 ± 5.1	37.6 ± 5.3	0.72
LVEF (%)	67.8 ± 6.2	69.2 ± 4.0	67.6 ± 6.5	0.28
Electrocardiographic parameters				
P-wave duration in lead II (ms)	121.8 ± 19.4	119.2 ± 19.6	122.1 ± 19.3	0.54
P-wave duration in lead V_1 (ms)	106.2 ± 18.0	108.8 ± 13.3	105.9 ± 18.5	0.49
QRS complex duration in lead II (ms)	89.1 ± 16.8	85.8 ± 15.3	89.4 ± 17.0	0.35
QRS complex duration in lead V_1(ms)	101.0 ± 16.1	98.0 ± 19.6	101.4 ± 15.7	0.37
QTc interval (ms)	419.0 ± 22.5	417.4 ± 23.5	419.4 ± 22.3	0.74
Laboratory parameters				
BNP level (pg/mL)	48.9 [22.9-96.7]	79.2 [30.8-183.7]	45.2 [22.3-85.4]	0.45
CCr (mL/min)	64.2 [53.1-77.9]	67.2 [49.3-80.7]	64.9 [53.3-77.8]	0.65
Underlying disease, n (%)				
Heart failure	10 (5.3)	1 (4.8)	9 (5.3)	0.91
Hypertension	98 (51.9)	11 (55.0)	87 (51.5)	0.77
Diabetes mellitus	19 (10.0)	2 (9.5)	17 (10.6)	0.94
Stroke	10 (5.3)	1 (4.8)	9 (5.4)	0.91
$CHADS_2$ score (points)	1 [0-2]	1 [0-2]	1 [0-2]	0.51
Procedure, n (%)				
PVI alone	159 (83.7)	15 (71.4)	144 (85.2)	0.11
PVI + other procedures	31 (16.3)	6 (28.6)	25 (14.8)	
Medication, n (%)				
β-blocker	65 (34.2)	10 (47.6)	55 (32.5)	0.17
RASI	71 (37.6)	6 (28.6)	65 (38.7)	0.37
MRA	7 (3.7)	1 (4.8)	6 (3.6)	0.78
Statin	49 (25.8)	5 (23.8)	44 (26.0)	0.83

Table1. Comparison of baseline characteristics between patients with and without recurrence

Values are presented as mean ± standard deviation, median with interquartile range, or n (%).
BMI: Body mass index, *LAD*: Left atrium diameter, *LVEF*: left ventricular ejection fraction, *BNP*: B-type natriuretic peptide, *CCr*: Creatinine clearance, *PVI*: Pulmonary vein isolation, *RASI*: Renin-angiotensin system inhibitor, *MRA*: Mineralocorticoid receptor antagonist

Table 2. P-SAECG findings of patients with or without recurrence

	Total n=190	Recurrence group n=21	Non-Recurrence group n=169	*P*-value
P-SAECG				
Positive ALP, n (%)	126 (66.3)	18 (85.7)	108 (63.9)	0.04

P-SAECG: P-wave signal-averaged electrocardiography, ALP: Atrial late potentials

Table 3. Independent predictors of atrial fibrillation recurrence

	OR (95% CI)	*P*-value
Female sex	2.53 (0.69-5.87)	0.06
PVI alone	0.50 (0.17-1.45)	0.20
Positive ALP	3.83 (1.05-14.05)	0.04

PVI: Pulmonary vein isolation, ALP: Atrial late potentials, CI: Confidence interval, OR: Odds ratio