



Long P-wave duration immediately after pulmonary vein isolation on radiofrequency catheter ablation for atrial fibrillation predicts clinical recurrence: correlation with atrial remodeling in persistent atrial fibrillation

Shiou Ohguchi^{1,2} · Yasuya Inden² · Satoshi Yanagisawa^{2,3} · Takuro Shigematsu¹ · Kenichiro Yasuda¹ · Ken Katagiri¹ · Mitsutoshi Oguri¹ · Toyoaki Murohara²

Received: 27 April 2021 / Accepted: 20 August 2021 / Published online: 25 August 2021
© Springer Japan KK, part of Springer Nature 2021

Abstract

P-wave morphology reflects atrial remodeling and indicates prognosis after radiofrequency catheter ablation (RFCA) for atrial fibrillation (AF). The impact of p-wave morphology after excluding the effect of pulmonary vein (PV) substrate on outcomes is unknown. We evaluated the p-wave morphology on electrocardiography immediately after PV isolation for clinical outcomes. Eighty-four consecutive patients (47 with paroxysmal AF and 37 with persistent AF) who underwent RFCA were included. P-wave duration (PWD) and amplitude in all leads were examined during sinus rhythm immediately after PV isolation. We evaluated the relationship between electrocardiogram parameters and AF recurrence, according to the type of AF and following ablation, and the correlation with left atrial (LA) volume, low voltage ratio, and fixed conduction time. During 12 months of follow-up, 20 patients experienced recurrence. The cut-off value of PWD > 120 ms in lead I showed a sensitivity of 75% and specificity of 69% for predicting recurrence. PWD was significantly correlated with LA volume, low voltage, and conduction velocity. Significantly higher recurrence rates were observed in patients with PWD > 120 ms than in those with PWD ≤ 120 ms ($p < 0.001$), and the difference was more pronounced in patients with persistent AF. Multivariate analysis demonstrated that PWD > 120 ms was independently associated with recurrence in the total population (hazard ratio 2.00; 95% confidence interval 1.27–3.22; $p = 0.003$) and in patients with persistent AF. In conclusion, long PWD after PV isolation predicts AF recurrence, which might be associated with the extent of the LA substrate in persistent AF.

Keywords P-wave duration · Atrial fibrillation · Catheter ablation · LA substrate, recurrence

Introduction

Radiofrequency catheter ablation (RFCA) is an effective method of rhythm control for atrial fibrillation (AF), and its success rate is approximately 70–80% with a single procedure [1]. Pulmonary vein (PV) isolation of AF has a

remarkable performance with maintaining sinus rhythm, because ectopic activity in PVs plays the important role of initiating and perpetuating AF [2]. However, there is often a problem of AF recurrence after RFCA, which is mainly because of PV reconnection or substrate remodeling of the left atrium (LA). LA remodeling refers to the spectrum of pathophysiological changes in atrial structure and mechanical and electric functions, which often becomes associated with an increased risk of cardiovascular and embolic events and mortality through an intervention of AF [3–5].

P-wave morphology on an electrocardiogram (ECG) can be a simple and non-invasive tool to reflect the process of electrical and structural remodeling, because its duration and amplitude can be associated with atrial conduction and the direction of atrial depolarization and myocardial mass. In particular, prolonged p-wave duration (PWD) has been

✉ Satoshi Yanagisawa
pinponstar@yahoo.co.jp

¹ Department of Cardiology, Kasugai Municipal Hospital, Kasugai, Japan

² Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

³ Department of Advanced Cardiovascular Therapeutics, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan

proven to represent AF-associated atrial structural alterations [6]. There are several studies in which pre-ablation p-wave morphology can be identified as a predictor of AF recurrence after PV isolation [6–12]. However, standard measurement of PWD on ECG can be calculated at the time of sinus rhythm only. The p-wave morphology during AF rhythm cannot be assessed before the procedure, and therefore, p-wave analysis is not possible prior to ablation in patients with persistent AF. By contrast, there are few prior studies investigating the relationship of post-ablation p-wave morphology with the procedure outcome [13, 14]. The p-wave could also change after catheter ablation because of the modification of atrial myocardial condition. In particular, the p-wave after PV isolation could reflect the remaining atrial substrate in the LA and be a potential marker for estimating LA substrate requiring additional ablation after PV isolation. It is unclear whether p-wave morphology could be a predictor of prognosis and a representative marker for the estimation of additional LA substrate after excluding the effect of arrhythmogenic PV substrate by catheter ablation.

Thus, this study aimed to investigate the relationship between p-wave morphology on ECG immediately after PV isolation and before additional substrate procedure with prognosis after ablation for AF, and to evaluate the correlation between p-wave morphology and LA volume, voltage substrate, and conduction velocity.

Material and methods

Study population

The present study retrospectively analyzed a catheter ablation database at Kasugai Municipal Hospital in Japan. A total of 84 consecutive patients with symptomatic, refractory AF who underwent RFCA for the first time between January 2017 and May 2018 were enrolled. The indication for catheter ablation is in accordance with recent guidelines [15]. All patients underwent preprocedural imaging study using contrast computed tomography (CT), in which replacement fluid was sometimes needed for patients with renal failure. Each three-dimensional (3D) LA anatomical structure was constructed with this imaging to prepare for catheter ablation and to measure prior LA volume. Transthoracic and transesophageal echocardiography were also performed to comprehend information, including the existence or absence of LA thrombus before the procedure. The exclusion criteria for this study were as follows: (i) severe valvular heart disease; (ii) previous RFCA treatment; (iii) follow-up period < 3 months after ablation; (iv) non-radiofrequency, cryoballoon ablation treatment; and (v) failure to restore sinus rhythm by cardioversion after PV isolation. This study was approved by our institutional ethics

committee. All patients provided written informed consent prior to the procedure. All examinations and procedures were performed in compliance with the principles of the Declaration of Helsinki.

Catheter ablation and postprocedural follow-up

Antiarrhythmic drugs (AADs) were discontinued for at least five half-lives before catheter ablation in all patients. All ablation procedures, including PV isolation, were performed under the guidance of the 3D-electroanatomical mapping system (CARTO, Biosense Webster) with LA geometry obtained from the CT image. We used a 3.5 mm tip, open-irrigated contact force sensing ablation catheter (25–35 W, 42 °C, irrigation flow rate of 17–30 mL/min; NaviStar ThermoCool SmartTouch, Biosense Webster, Inc.), a circular mapping catheter (Lasso, Biosense Webster, Inc.), and a multi-electrode mapping catheter (PentaRay, Biosense Webster, Inc.). The contact force of the catheter was targeted at 10–25 g, and catheter stability was set with a force–time integral of > 100 g*s. PV isolation was confirmed by the elimination of PV potentials as recorded by a circular mapping catheter and the bi-directional electrical block between the LA and PV. When AF rhythm persisted after PV isolation, external cardioversion was performed to restore sinus rhythm. In addition to circumferential PV isolation, cavotricuspid isthmus (CTI) ablation was applied to prevent a typical common atrial flutter, if necessary. After the procedure, atrial arrhythmia was introduced by rapid atrial stimulus pacing with a high dose of isoproterenol infusion, and then focal ablation for extra PV origin and linear ablation were added for the provoked AF or atrial flutter, if necessary.

All patients were followed-up through the outpatient clinic for 1 year after discharge and were checked for AF recurrence. They were instructed to see their attending physician 1–2 weeks and 1 month after discharge, and thereafter, every 3 months for 1 year. At each follow-up consultation, they underwent 12-lead surface ECG and were asked if they had any symptoms related to the presence of arrhythmia. Twenty-four-hour Holter monitoring was also performed at least 1, 3, and 12 months after discharge. AF recurrence was defined as an episode of AF or atrial tachycardia lasting 30 s or longer after a blanking period of 3 months following the procedure.

P-wave analysis on 12-lead surface ECG

P-wave morphology was examined during sinus rhythm immediately after PV isolation and CTI ablation and before the intravenous infusion of isoproterenol and pacing stimulation. “Post-ablation” p-wave on surface ECG was analyzed with a paper speed of 100 mm/s and more than 32 mm/mV (BARD LabSystem Pro EP; Boston Scientific). The signal

from each lead was filtered through a setting between 0.1 and 100 Hz. P-wave morphology in the limbs and precordial leads was analyzed by an experienced investigator who was completely blinded to the outcomes and patient characteristics. The p-wave amplitude (PWA) was measured from the wave's peak or nadir to the isoelectric line, and the PWD was measured between the p-wave's beginning and end based on the isoelectric line. The p-wave in lead V1 is pronouncedly biphasic compared with the other leads, and it was divided into positive and negative wave portions based on the isoelectric line, which were evaluated for the outcomes in previous reports [16–18]. On the other hand, the parameters in other leads were unified as a simple morphology to be measured using the conventional one.

Measurement of LA volume in CT image

All CT scans were performed on a 64-slice scanner before RFCA. Radiocontrast amount adjusted by the patient's body weight was administered in 25–30 s. Subsequently, a 3D image, including the LA and PVs, was created, and the final image was constructed to measure LA volume after excluding all PVs.

Measurement of LA local conduction

Post-ablation LA conduction time was measured immediately after PV isolation during sinus rhythm by inserting a fixed electrode catheter (BeeAT, Japan Life Line) into the coronary sinus (CS). This conduction time could represent a local conduction velocity through the fixed distance of the electrode catheter. The proximal side of the electrode catheter was placed at the ostium of the coronary sinus. The time delay between the beginning of the proximal and distal electrode potentials on the four continuous electrodes of the catheter was measured using the LabSystem as described above [19]. In this calculation, the potentials of the four continuous electrodes should have had the same polarity to avoid collision sites of two different conduction in this local area.

Measurement of LA low voltage ratio

An LA voltage map was generated with bipolar electrograms in the multi-electrode mapping catheter (PentaRay, Biosense Webster, Inc.) with 800–1200 points during sinus rhythm after PV isolation. The introduction of atrial arrhythmia by isoproterenol and pacing stimulation was performed after creating the whole voltage map in the LA in all cases. The low-voltage area was defined as an amplitude of <0.5 mV, and the ratio of the low-voltage area to LA area was calculated using an area measurement software equipped with the CARTO system.

Statistical analyses

Continuous data are expressed as means \pm standard deviations, and categorical parameters are presented as numbers (percentages). Comparison of the baseline characteristics and ECG parameters between the recurrence and non-recurrence groups was assessed using Student's *t* tests for continuous values and χ^2 tests or Fisher's exact test for categorical values. Intra-class correlation coefficient estimates were used to assess the intra- and inter-observer reproducibility of the ECG parameter measurements. The receiver-operating characteristic (ROC) curves for each parameter were plotted, and the areas under the curves (AUCs) were compared. The cut-off value of the AF recurrence in the parameter was determined based on the ROC curve. Kaplan–Meier survival curve analysis was used to estimate the prognosis, and the difference in the curves was assessed using a log-rank test. The prognostic value of each factor was first evaluated using univariate Cox regression analysis. Significant factors in the univariate analysis were entered into a multivariate Cox regression model to identify independent predictors. Pearson's correlation coefficient analysis was used to evaluate the relationship between ECG parameters and each LA remodeling parameter. A *p* value of <0.05 was considered statistically significant. Statistical analysis was performed with JMP (JMP, SAS Institute Inc., Cary, NC, USA).

Results

Baseline patient characteristics in patients with and without recurrence of AF

In the total population ($n = 84$), 20 patients had recurrence during the 1 year follow-up period after ablation. Table 1 shows the comparison of clinical characteristics between patients with and without AF recurrence 1 year after ablation. The recurrence group had a significantly larger LA diameter and LA volume than the non-recurrence group. No significant differences in other factors, including the type of AF, comorbidities, and CHADS2 and CHA2DS2-VASc scores, were observed between the two groups.

Among the total population, 47 patients had paroxysmal AF, while 37 patients had persistent AF. Recurrence occurred in 8 patients (17%) with paroxysmal AF and 12 (32%) with persistent AF. Table 2 shows the baseline characteristics of the recurrence and non-recurrence groups for each type of AF. A history of heart failure was more frequent, and the CHADS2 score was significantly higher in the recurrence group than in the non-recurrence group in patients with paroxysmal AF. By contrast, LA volume was larger in the recurrence group than in the non-recurrence group in patients with persistent AF. The recurrence

Table 1 Baseline characteristics in the clinical recurrence and non-recurrence groups

Parameters	No clinical recurrence N = 64	Clinical recurrence N = 20	P value
Age (years)	67.3 ± 8.2	67.7 ± 8.8	0.835
Gender (male/female, %)	65.6/34.4	85.0/15.0	0.098
Body mass index (kg/m ²)	23.9 ± 5.1	23.3 ± 6.6	0.693
Current or former smoker (%)	36 (56.3)	15 (75.0)	0.134
Persistent AF (%)	25 (39.1)	12 (60.0)	0.100
Open heart surgery (%)	0 (0.0)	1 (5.0)	0.238
Comorbidity			
Type 2 diabetes mellitus (%)	8 (12.5)	4 (20.0)	0.307
Hypertension (%)	37 (57.8)	12 (60.0)	0.862
Dyslipidemia (%)	23 (35.9)	6 (30.0)	0.626
Chronic kidney disease (%)	12 (18.8)	3 (15.0)	0.497
Coronary artery disease (%)	2 (3.1)	3 (15.0)	0.085
Congestive heart failure (%)	14 (21.9)	7 (35.0)	0.237
Previous stroke (%)	10 (15.6)	6 (30.0)	0.136
CHADS ₂ score	1.4 ± 1.2	2.0 ± 0.9	0.056
CHA ₂ DS ₂ -VASc score	2.4 ± 1.5	3.1 ± 1.3	0.051
Medication at admission (%)			
ACE inhibitor or ARB (%)	21 (32.8)	7 (35.0)	1.000
Beta-blocker (%)	23 (35.9)	9 (45.0)	0.564
Echocardiography			
LA dimension (mm)	39.3 ± 5.5	42.9 ± 6.1	0.013
LV ejection fraction (%)	65.4 ± 11.7	67.1 ± 11.0	0.633
E/e'	11.6 ± 3.5	11.4 ± 3.1	0.846
Primary measurements			
LA volume (mL)	129.8 ± 32.6	162.1 ± 38.7	<0.001
Local LA conduction time (ms)	62.8 ± 8.2	71.3 ± 6.9	<0.001
LA low voltage ratio (%)	9.6 ± 13.2	15.8 ± 12.5	0.089

ACE angiotensin converting enzyme, ARB angiotensin II receptor blocker, LA left atrium

group exhibited a longer local conduction time than the non-recurrence group both in paroxysmal AF and persistent AF. A comparison of the ablation procedure between the recurrence and non-recurrence groups according to the type of AF is shown in Table 3. PV isolation was successfully achieved in all patients. Thirteen patients (28%) with paroxysmal AF and 23 patients (62%) with persistent AF required additional ablation after PV isolation and CTI ablation. The recurrence rate between the additional ablation and non-additional ablation groups was observed in 2/13 (15%) and 6/34 (18%) patients with paroxysmal AF ($p > 0.999$),

and 10/23 (43%) and 2/14 patients (14%) with persistent AF ($p = 0.088$), respectively. No significant difference in individual procedure outcomes was observed between the recurrence and non-recurrence groups in both the paroxysmal AF and persistent AF groups.

Electrocardiogram characteristics for the prognosis after ablation

Table 4 shows the comparison of the ECG characteristics of the PWD and PWA in all leads between the recurrence and non-recurrence groups. The recurrence group showed a significantly longer PWD in lead I (125.4 ± 12.9 vs. 113.8 ± 11.3 ms, $p < 0.001$), II ($p = 0.003$), III ($p = 0.006$), aVR ($p = 0.005$), and aVF ($p = 0.021$) than did the non-recurrence group. There was no significant difference in PWA among all leads between the two groups. Intra- and inter-observer correlation coefficients of the PWD involving leads I, II, III, aVR, and aVF in 30 patients who were randomly selected from the study population were 0.76 [95% confidence interval (CI) 0.56–0.88; $p < 0.001$] and 0.75 (95% CI 0.55–0.87; $p < 0.001$), respectively.

Assessment of PWD and its impact on the outcome after ablation according to the cut-off value

We selected five ECG values (PWDs in lead I, II, III, aVR, and aVF) showing a significant association with AF recurrence after ablation, which were presumed reliable parameters for predicting the risk of AF recurrence, and further assessed each property to detect the most useful parameter with a cut-off value on the ROC analysis. Among the five ECG parameters, the ROC curve analysis identified PWD in lead I as the most reliable parameter for predicting AF recurrence after RFCA, with the highest AUC of 0.76 (Fig. 1). The cut-off value of PWD in lead I was determined to be 120 ms, based on the ROC curve with a sensitivity of 75% and specificity of 69% for predicting AF recurrence. Kaplan–Meier survival curve analysis demonstrated a significantly lower rate of AF event-free survival after ablation in patients with PWD > 120 ms than in those with PWD ≤ 120 ms in the entire study population ($p < 0.001$, Fig. 2).

Predictive value of PWD in lead I

In the entire study population, univariate Cox regression analysis identified LA diameter [hazard ratio (HR) 1.10; 95% CI 1.02–1.18; $p = 0.013$] and PWD in lead I > 120 ms (HR 2.15; 95% CI 1.38–3.44; $p = 0.001$) as significant parameters for AF recurrence following ablation. On multivariate analysis, LA diameter (HR 1.08; 95% CI 1.00–1.16; $p = 0.049$) and the PWD in lead I > 120 ms (HR 2.00; 95%

Table 2 Comparison of the baseline characteristics between the recurrence and non-recurrence groups in patients with paroxysmal AF and persistent AF

Parameters	Paroxysmal AF (N = 47)			Persistent AF (N = 37)		
	No clinical recurrence N = 39	Clinical recurrence N = 8	P value	No clinical recurrence N = 25	Clinical recurrence N = 12	P value
Age (years)	68.2 ± 7.5	65.6 ± 12.2	0.434	64.7 ± 9.8	69.1 ± 5.9	0.165
Gender (male/female, %)	59.0/41.0	87.5/12.5	0.129	80.0/20.0	83.3/16.7	0.594
Body mass index (kg/m ²)	24.3 ± 4.8	24.7 ± 6.5	0.837	23.2 ± 5.5	22.4 ± 6.8	0.710
Current or former smoker (%)	19 (48.7)	6 (75.0)	0.167	18 (72.0)	9 (75.0)	0.588
Comorbidity						
Type 2 diabetes mellitus (%)	5 (12.8)	1 (12.5)	0.733	3 (12.0)	3 (25.0)	0.290
Hypertension (%)	22 (56.4)	5 (62.5)	0.535	14 (56.0)	7 (58.3)	0.893
Dyslipidemia (%)	17 (43.6)	1 (12.5)	0.103	5 (20.0)	5 (41.7)	0.160
Chronic kidney disease (%)	5 (12.8)	1 (12.5)	0.733	7 (28.0)	2 (16.7)	0.376
Coronary artery disease (%)	1 (2.6)	1 (12.5)	0.315	1 (4.0)	2 (16.7)	0.241
Congestive heart failure (%)	4 (10.3)	5 (62.5)	0.004	10 (40.0)	2 (16.7)	0.148
Previous stroke (%)	5 (12.8)	2 (25.0)	0.340	4 (16.0)	4 (33.3)	0.136
CHADS ₂ score	1.2 ± 1.0	2.1 ± 0.8	0.021	1.6 ± 1.3	1.8 ± 1.0	0.588
CHA ₂ DS ₂ -VASc score	2.3 ± 1.3	3.0 ± 1.1	0.150	2.4 ± 1.7	3.2 ± 1.4	0.186
Medication at admission (%)						
ACE inhibitor or ARB (%)	17 (43.6)	3 (37.5)	0.511	11 (44.0)	7 (58.3)	0.278
Beta-blocker (%)	16 (41.0)	5 (62.5)	0.254	16 (64.0)	5 (41.7)	0.250
Echocardiography						
LA dimension (mm)	37.3 ± 4.4	41.5 ± 7.4	0.156	42.1 ± 5.8	43.8 ± 5.3	0.390
LV ejection fraction (%)	70.3 ± 8.9	68.3 ± 12.9	0.582	57.9 ± 16.4	66.3 ± 10.1	0.114
E/e'	11.9 ± 3.9	11.5 ± 2.5	0.820	11.0 ± 2.8	11.3 ± 3.6	0.757
Primary measurements						
LA volume (mL)	120.3 ± 29.8	144.2 ± 39.0	0.057	144.7 ± 31.7	174.1 ± 35.0	0.015
Local LA conduction time (ms)	62.8 ± 8.7	70.0 ± 6.3	0.034	62.8 ± 7.6	72.2 ± 7.5	0.002
LA low voltage ratio (%)	7.5 ± 4.9	13.3 ± 11.9	0.255	12.9 ± 20.0	17.6 ± 13.2	0.502

ACE angiotensin converting enzyme, ARB angiotensin II receptor blocker, LA left atrium

CI 1.27–3.22; $p=0.003$) remained independent predictors for AF recurrence (Table 5).

Predictive value of PWD in lead I according to the type of AF and following ablation strategy

The population was divided into patients with paroxysmal AF and persistent AF, and predictors of recurrence were evaluated in each group. Among the patients with persistent AF, the cut-off value of PWD in lead I was determined to be 120 ms for predicting AF recurrence, which was similar to the value analyzed in the total study population. PWD in lead I > 120 ms was the only significant predictor for AF recurrence (HR 3.35; 95% CI 1.70–8.57; $p < 0.001$) on univariate analysis. By contrast, a history of heart failure (HR 2.65; 95% CI 1.24–6.05; $p = 0.013$) was the predictor of recurrence in patients with paroxysmal AF (Table 6). PWD

was not significantly associated with recurrence of AF in patients with paroxysmal AF.

The population was divided into four groups according to the type of AF and cut-off value of PWD > 120 ms in lead I, and the prognosis of the recurrence was compared among the four groups. Patients with persistent AF and PWD > 120 ms showed the lowest rate of AF event-free survival in comparison with that of the other groups (Supplementary Fig. 1). Furthermore, the total population was alternatively classified into four groups according to the requirement of additional ablation and the cut-off value of PWD in lead I, and the prognosis was similarly compared among the groups. Of note, patients with PWD > 120 ms had a higher rate of AF recurrence regardless of the additional ablation procedure in the Kaplan–Meier survival curve analysis (Supplementary Fig. 2).

When focusing on the group without additional ablation ($n=48$) meaning a single PV isolation procedure, the cut-off

Table 3 Procedural parameters in the clinical recurrence and non-recurrence groups

Parameters	No clinical recurrence N = 64	Clinical recurrence N = 20	P value
<i>Ablation procedures</i>			
Paroxysmal AF	39	8	
Pulmonary vein isolation (%)	39 (100.0)	8 (100.0)	n/a
LA linear ablation (%)	1 (2.6)	0 (0.0)	0.830
Mitral isthmus ablation (%)	1 (2.6)	0 (0.0)	0.830
SVC isolation (%)	1 (2.6)	0 (0.0)	0.830
Non-PV foci ablation (%)	8 (20.5)	2 (25.0)	0.550
Cavotricuspid isthmus ablation (%)	35 (89.7)	7 (87.5)	0.625
Other additional ablation (%)	0 (0.0)	0 (0.0)	n/a
Persistent AF	25	12	
Pulmonary vein isolation (%)	25 (100.0)	12 (100.0)	n/a
LA linear ablation (%)	6 (24.0)	4 (33.3)	0.412
Mitral isthmus ablation (%)	2 (8.0)	2 (16.7)	0.391
SVC isolation (%)	0 (0.0)	1 (8.3)	0.324
Non-PV foci ablation (%)	5 (20.0)	3 (25.0)	0.520
Cavotricuspid isthmus ablation (%)	19 (76.0)	11 (91.7)	0.253
Other additional ablation (%)	0 (0.0)	0 (0.0)	n/a
Procedure time (min)	226.1 ± 50.4	227.0 ± 39.1	0.942

AF atrial fibrillation, LA left atrium, PV pulmonary vein, SVC superior vena cava

value of PWD in lead I for recurrence ($n = 8$) was 122 ms. The PWD in lead I > 122 ms (HR 1.86; 95% CI 1.06–3.28; $p = 0.029$), CHADS2 score (HR 1.76; 95% CI 1.09–2.78; $p = 0.022$), and LA diameter (HR 1.10; 95% CI 1.01–1.20; $p = 0.036$) were significant predictors for AF recurrence in the univariate analysis.

Relation between PWD and other LA remodeling measurements

As described earlier, LA volume, LA local conduction time, and LA low voltage ratio were measured as possible correlative remodeling parameters with PWD. In the total study population, PWD in lead I was significantly correlated with LA volume on 3D-CT ($r = 0.394$, $p < 0.001$) and conduction time velocity ($r = 0.451$; $p < 0.001$), and was mildly correlated with LA low voltage ratio ($r = 0.273$, $p = 0.017$) (Fig. 3). The population was divided into sub-groups of paroxysmal AF and persistent AF, and the correlation was similarly evaluated in each group. Significant correlations were observed between PWD and LA volume ($r = 0.591$, $p = 0.017$) and conduction time velocity ($r = 0.424$; $p = 0.011$) in patients with persistent AF (Fig. 4). By contrast, the PWD was significantly correlated with conduction time velocity ($r = 0.465$, $p = 0.001$) and LA low voltage ratio ($r = 0.491$, $p < 0.001$) in patients with paroxysmal AF. We further evaluated the correlation between patients with additional ablation and those without. Both groups exhibited a

significant relationship between PWD and LA remodeling parameters (Fig. 5).

The ROC curve analyses to assess the prognostic value of LA volume, LA conduction time, and low voltage ratio for the risk of AF recurrence showed an AUC of 0.74 and a cut-off value of 153.0 mL with a sensitivity of 70% and specificity of 78% in LA volume; an AUC of 0.79, and a cut-off value of 66 ms with a sensitivity of 84% and specificity of 63% in LA conduction time; and an AUC of 0.67 and a cut-off value of 15.7% with a sensitivity of 53% and specificity of 90% in LA low voltage ratio (Fig. 6), respectively.

Discussion

The major findings of the present study are as follows: (i) prolonged PWD on ECG immediately after PV isolation was significantly related to the clinical recurrence of AF after RFCA, (ii) the prognostic value of PWD was stronger in patients with persistent AF than in those with paroxysmal AF, (iii) the longer PWD in lead I was significantly correlated with enlarged LA volume and delayed LA conduction, and (iv) the prognostic value of the longer PWD was definitive for recurrence regardless of the application of ablation in addition to PV isolation.

Many studies have indicated the association of p-wave morphology in ECG with AF recurrence after catheter ablation. A statistically significant difference was reported between the mean PWD of subjects with recurrent AF and

Table 4 Comparison of the ECG parameters in all leads between the recurrence and non-recurrence groups

Parameters	No clinical recurrence N = 64	Clinical recurrence N = 20	P value
P-wave duration (ms)			
Lead I	113.8 ± 11.3	125.4 ± 12.9	<0.001
Lead II	117.9 ± 15.2	129.9 ± 15.2	0.003
Lead III	117.3 ± 10.8	128.7 ± 15.6	0.006
Lead aVR	120.5 ± 11.6	129.6 ± 14.9	0.005
Lead aVL	119.1 ± 9.8	126.1 ± 15.9	0.073
Lead aVF	120.0 ± 11.4	129.7 ± 16.5	0.021
Lead V1 (pos)	54.0 ± 15.6	61.1 ± 18.5	0.092
Lead V1 (neg)	64.3 ± 17.0	69.1 ± 18.5	0.297
Lead V2	98.5 ± 17.3	97.4 ± 17.4	0.862
Lead V3	105.4 ± 17.8	101.9 ± 16.2	0.626
Lead V4	112.2 ± 19.3	110.1 ± 16.7	0.497
Lead V5	117.7 ± 19.2	116.6 ± 19.4	0.827
Lead V6	119.9 ± 17.2	118.3 ± 17.9	0.725
P-wave amplitude (mV)			
Lead I	0.041 ± 0.019	0.040 ± 0.019	0.702
Lead II	0.097 ± 0.038	0.092 ± 0.029	0.569
Lead III	0.078 ± 0.035	0.070 ± 0.019	0.287
Lead aVR	0.061 ± 0.027	0.058 ± 0.016	0.588
Lead aVL	0.033 ± 0.018	0.035 ± 0.017	0.619
Lead aVF	0.086 ± 0.034	0.078 ± 0.023	0.315
Lead V1 (pos)	0.067 ± 0.045	0.065 ± 0.041	0.929
Lead V1 (neg)	0.063 ± 0.029	0.073 ± 0.040	0.203
Lead V2	0.086 ± 0.044	0.094 ± 0.043	0.500
Lead V3	0.088 ± 0.039	0.084 ± 0.035	0.623
Lead V4	0.079 ± 0.031	0.072 ± 0.022	0.356
Lead V5	0.067 ± 0.030	0.060 ± 0.020	0.277
Lead V6	0.058 ± 0.023	0.049 ± 0.016	0.098

ECG electrocardiogram

those without. In particular, PWD in 12-lead ECG pre-ablation was analyzed in most cases, where the cut-off value was reported to range from 120 to 140 ms [7]. Caldwell et al. studied PWD pre-ablation among paroxysmal AF undergoing PV isolation and reported that PWD > 140 ms predicted AF recurrence with an OR of 2.41 [10]. Mugnai et al. reported a PWD > 120 ms as a predictor of recurrence in patients with drug-resistant symptomatic paroxysmal AF and normal left atrial size [6]. Wu et al. also demonstrated that patients with paroxysmal AF having advanced interatrial block were at an increased risk of AF recurrence after catheter ablation, and defined it as a PWD > 120 ms and biphasic morphology in inferior leads [8]. Among these studies, PWD was identified as the longest PWD in all leads obtained from 12-lead ECG. The cut-off points were different from each other, which was, however, a priori defined. However, our study is unique from the perspective of clinical utility in

calculating the cut-off value based on the ROC curves plotted and comparing the AUCs in all leads to scientifically investigate the most reliable value.

As these previous reports indicated, the p-wave morphology of sinus rhythm before ablation was considered to play an important role in predicting the outcome and degree of severity of AF. However, there are few studies that have analyzed the “post-ablation” p-wave morphology. The PWD could change with its morphology after PV isolation. Nakatani et al. determined the coefficient of variation of PWD as an index of atrial conduction heterogeneity with 12-lead ECG and demonstrated that it significantly decreased after catheter ablation in AF-free patients [14]. Other studies reported significantly decreased PWD on the surface ECG as well as signal-averaged ECG and the disappearance of notched p-wave after catheter ablation [11, 20]. Although the pathogenesis of p-wave modification after catheter ablation, such as decreased PWD, is unclear, one possible reason is that it may be caused by the shortening of conduction distance after electrical elimination of the PV. The conductance of the PV area can create atrial late potentials in the p-wave, which indicates prolonged PWD in patients with AF [21]. This hypothesis may also indicate that p-wave morphology analyzed after PV isolation may lead to a more accurate reflection of LA electrical condition except for the component of the PV muscle sleeves. Several studies have verified the relation of p-wave morphologic characteristics with LA remodeling factors, including voltage substrate, conduction, anatomy, stratification of AF, and AF burden [22, 23]. The PWD was also correlated with LA enlargement and volume index, which were measured by M-mode or 3D transthoracic echocardiography [24–26]. However, the former studies did not examine the p-wave morphology while focusing on patients with AF scheduled for catheter ablation. In this regard, the PWD immediately after PV isolation examined in the present study may be an accurate marker for representing LA remodeling, which was shown to have a significant correlation with LA low voltage ratio, volume, and conduction time velocity in the total population.

Of interest, the difference in AF free-survival according to the cut-off value of 120 ms for PWD in lead I was more pronounced in persistent AF than in paroxysmal AF. This could be because progressive pathology of persistent AF comes mainly from the LA substrate, and p-wave morphology after PV isolation may strongly reflect uncorrupted LA substrate conditions as mentioned earlier [27]. By contrast, most patients with paroxysmal AF generally have a less damaged, healthy myocardium in the LA after excluding that in PV sleeves. One possible reason why Jadidi et al. could show a strong significance between PWD and several LA remodeling outcomes is because of the inclusion of patients with persistent AF only [28]. It is plausible that PWD immediately after PV isolation had a positive correlation with LA

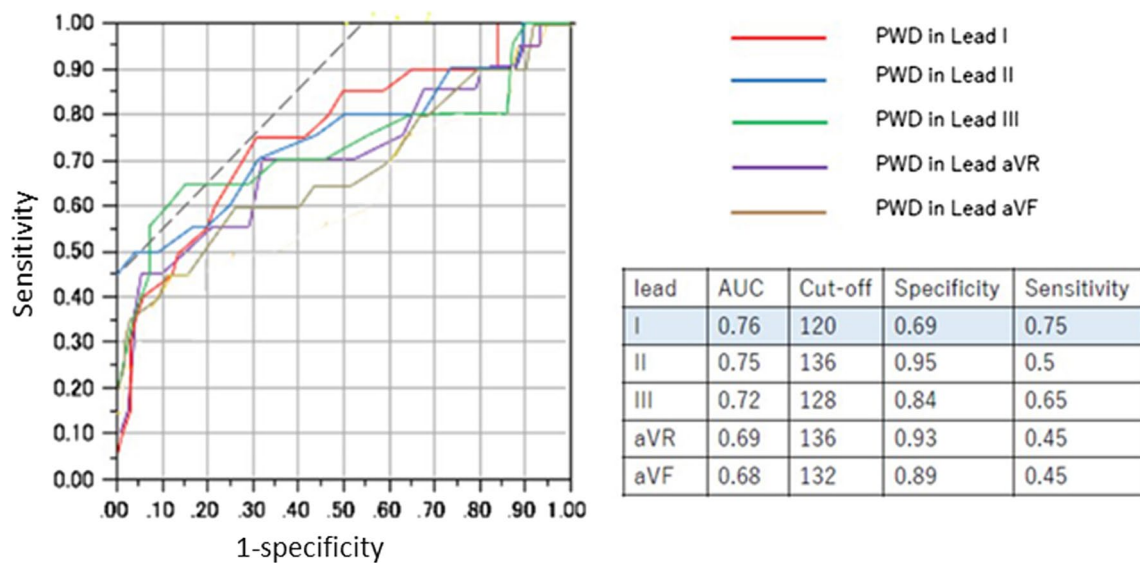
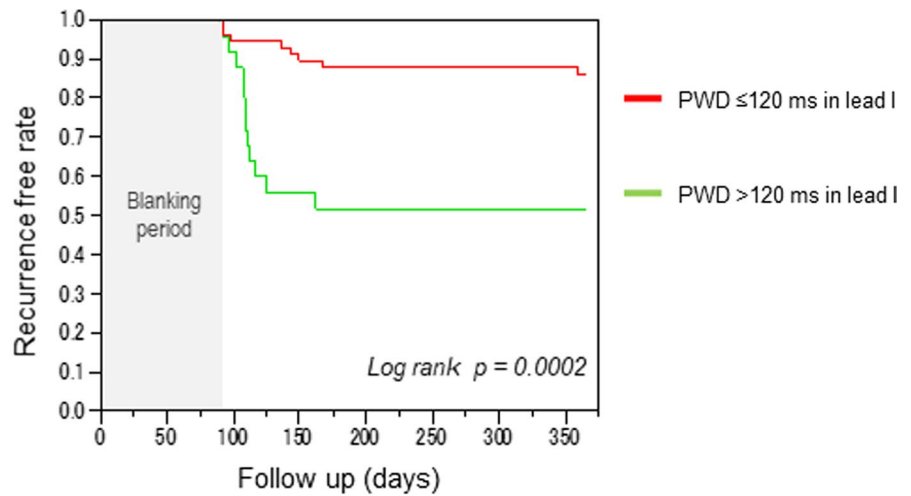


Fig. 1 The receiver-operating characteristic curves of the PWD in lead I, II, III, aVR, and aVF, which were found to be significant factors for the recurrence after ablation. *AUC* area under the curve, *PWD* p-wave duration

Fig. 2 Comparison of the Kaplan–Meier survival curves of AF-free survival after the ablation between patients with $PWD \leq 120$ ms in lead I and those with $PWD > 120$ ms. *AF* atrial fibrillation, *PWD* p-wave duration



Number of patients at risk				
$PWD \leq 120$ ms	59	57	52	52
$PWD > 120$ ms	25	23	13	13

Table 5 Predictors of clinical recurrence after ablation in the total study population in univariate and multivariable Cox regression analyses

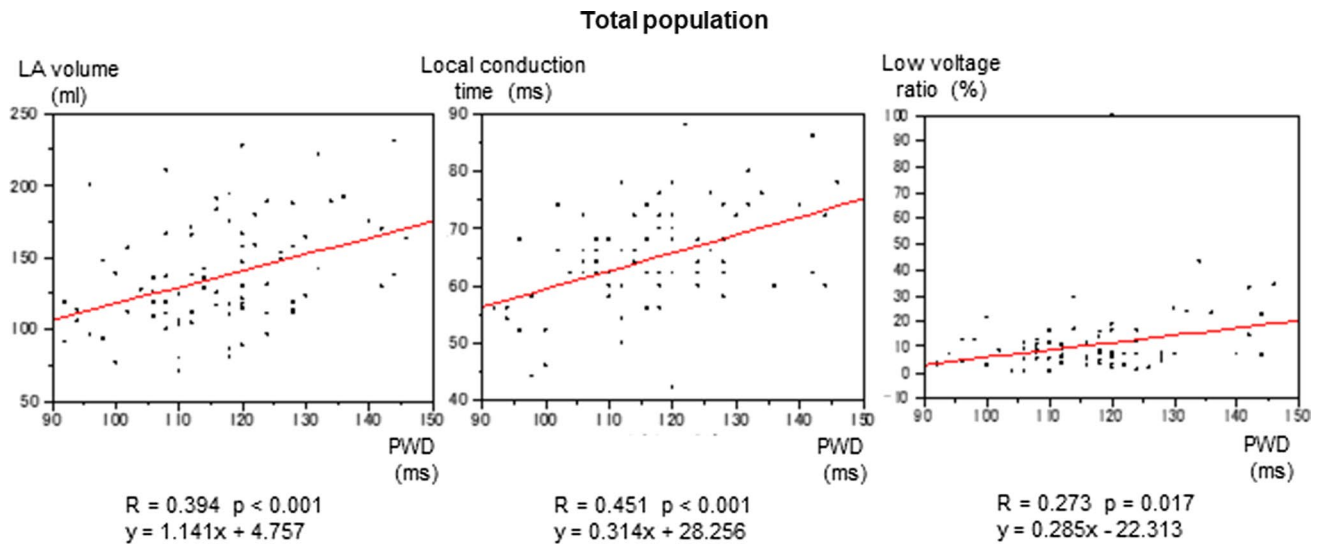
Parameters	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Left atrial diameter (mm)	1.10 (1.02–1.18)	0.013	1.08 (1.00–1.16)	0.049
PWD in lead I > 120 ms	2.15 (1.38–3.44)	0.001	2.00 (1.27–3.22)	0.003

CI confidence interval, *HR* hazard ratio, *PWD* p-wave duration

Table 6 Predictors of clinical recurrence after ablation in patients with paroxysmal AF and persistent AF in univariate and multivariate Cox regression analyses

Parameters	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Paroxysmal AF				
History of heart failure	3.07 (1.51–6.80)	0.002	2.65 (1.24–6.05)	0.013
Left atrial diameter (mm)	1.16 (1.02–1.32)	0.025		
Persistent AF				
PWD in lead I >120 ms	3.35 (1.70–8.57)	<0.001		

AF atrial fibrillation, CI confidence interval, HR hazard ratio, PWD p-wave duration

**Fig. 3** Correlations of the PWD in lead I with LA volume, LA conduction time, and LA low voltage ratio in the total population. LA left atrium, PWD p-wave duration

conduction time velocity and especially with LA volume in patients with persistent AF. In addition, PWD in patients with paroxysmal AF had a positive correlation with LA conduction time velocity and LA voltage ratio. It is speculated that anatomic factors might surpass electrical factors in the PWD analysis of persistent AF. There is still no study indicating what the p-wave morphology reflects according to remodeling progression, and this should be examined for future issues.

The present study showed a significantly poor outcome in patients with PWD > 120 ms, regardless of the additional ablation procedure. Moreover, there was a significant relationship between prolonged PWD and AF recurrence in patients undergoing PV isolation without any additional ablation for LA. The significant correlation between the

PWD and LA remodeling parameters in the additional and non-additional ablation groups might indicate that the PWD immediately after PV isolation might be a parameter for LA remodeling and an additional ablation strategy. In this context, using the PWD measurement immediately after PV isolation in addition to the conventional strategy of isoproterenol infusion and pacing stimulation might contribute to clinical outcomes. Our results may have a possible clinical implication of PWD assessment for estimating outcomes and deciding an additional ablation after PV isolation. A further prospective investigation with a large sample size will be required to validate PWD following PV isolation and the need for additional ablation in the future.

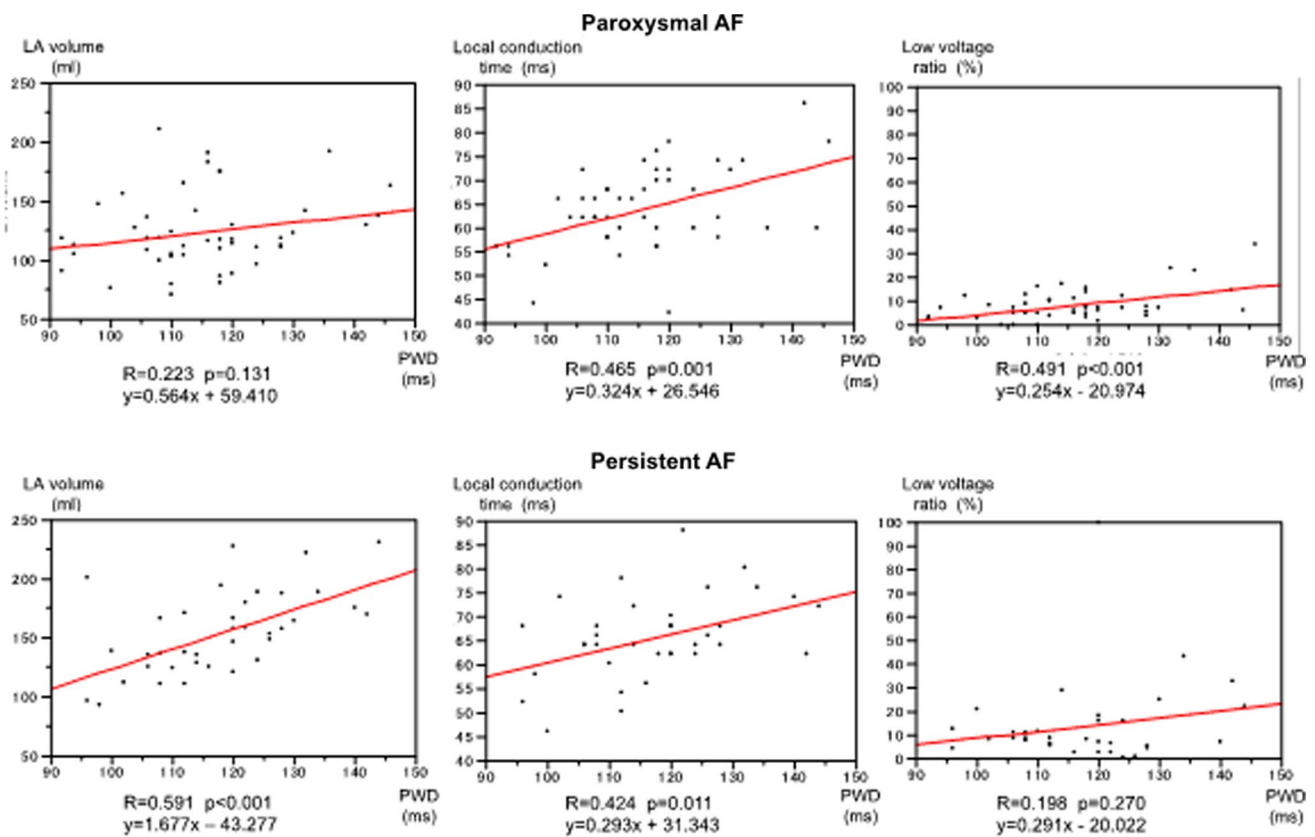


Fig. 4 Correlations of the PWD in lead I with LA volume, LA conduction time, and LA low voltage ratio in patients with paroxysmal and persistent AF. *LA* left atrium, *PWD* p-wave duration

Study limitations

This was a retrospective study conducted in a single institution. The number of patients enrolled in this study was relatively small. Although p-wave morphology generally reflects both left and right atrial electrical properties, the analysis of atrial volume, low voltage, and conduction time was performed only in the LA in our study. Conduction time was also calculated during sinus rhythm, not under CS proximal pacing, which could not eliminate the influence of activation through the Bachmann bundle. We studied post-ablation p-wave characteristics in patients with paroxysmal and persistent AF undergoing RFCA, and most patients with persistent AF were required to undergo cardioversion after PV isolation. However, cardiac electrophysiological properties after cardioversion are still controversial. The parameters of the p-wave were measured manually, and concern of the

measurement variability could remain despite the moderate correlation of inter- and intra-observer variability shown in this study. Because of the limited performance of follow-up examinations (e.g., 12-lead ECG, 24 h Holter monitoring), rhythm assessment in our study could cause underestimation of AF recurrence.

Conclusions

PWD in lead I immediately after PV isolation was the most reliable parameter to predict AF recurrence. In persistent AF, the prognostic value of this parameter was strongly found and might be associated with the extent of the LA substrate. It could also be the prior method for deciding the ablation strategy with the recent developed approaches and management of AF vulnerability [4, 5, 29, 30].

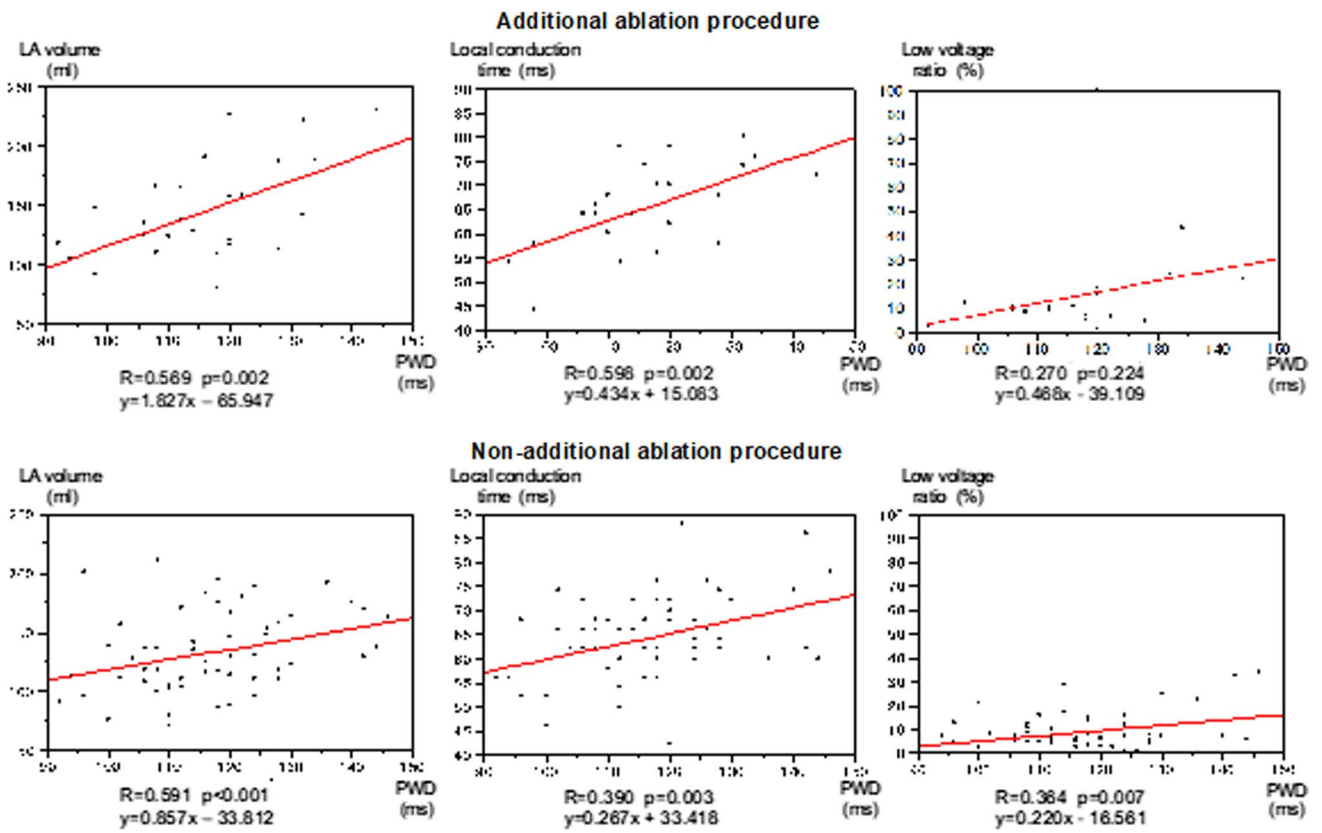


Fig. 5 Correlations of the PWD in lead I with LA volume, LA conduction time, and LA low voltage ratio in patients with additional ablation and those without. *LA* left atrium, *PWD* p-wave duration

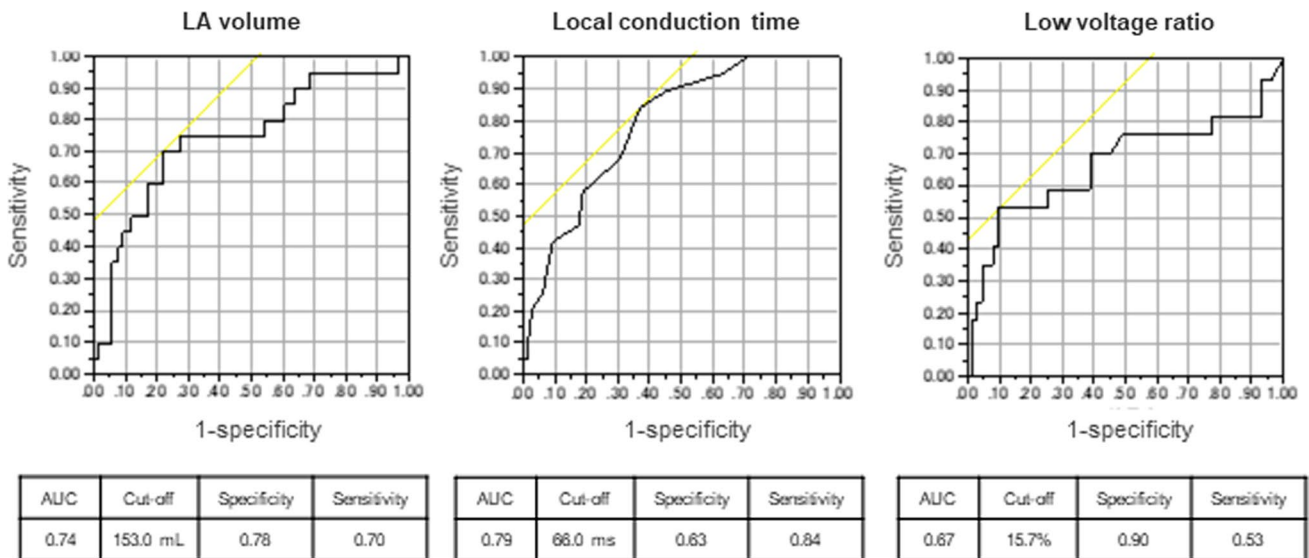


Fig. 6 ROC curve analyses to assess prognostic value of LA volume, LA conduction time, and low voltage ratio for the risk of AF recurrence. *AF* atrial fibrillation, *AUC* area under the curve, *LA* left atrium, *ROC* receiver-operating characteristic

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00380-021-01932-w>.

Acknowledgements None.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations

Conflict of interest Dr. Yanagisawa is affiliated with a department sponsored by Medtronic Japan. All other authors declare that there are no conflicts of interest.

Ethical approval This study was approved by local institutional ethics committee at Kasugai Municipal Hospital.

Consent to participate All patients provided written informed consent prior to the procedure.

References

- Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, d'Avila A, de Groot N, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T (2017) 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm* 14:e275–e444
- Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quinon G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J (1998) Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 339:659–666
- Hoit BD (2014) Left atrial size and function: role in prognosis. *J Am Coll Cardiol* 63:493–505
- Boriani G, Vitolo M, Diemberger I, Proietti M, Valenti AC, Malavasi VL, Lip GYH (2021) Optimizing indices of AF susceptibility and burden to evaluate AF severity, risk and outcomes. *Cardiovasc Res*. <https://doi.org/10.1093/cvr/cvab147>
- Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL (2021) 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 42:373–498
- Mugnai G, Chierchia GB, de Asmundis C, Julia J, Conte G, Sieira-Moret J, Capulzini L, Wauters K, Rodriguez-Manero M, Ciconte G, Baltogiannis G, Di Giovanni G, Saitoh Y, Brugada P (2016) P-wave indices as predictors of atrial fibrillation recurrence after pulmonary vein isolation in normal left atrial size. *J Cardiovasc Med (Hagerstown)* 17:194–200
- Pranata R, Yonas E, Vania R (2019) Prolonged P-wave duration in sinus rhythm pre-ablation is associated with atrial fibrillation recurrence after pulmonary vein isolation-A systematic review and meta-analysis. *Ann Noninvasive Electrocardiol* 24:e12653
- Wu JT, Long DY, Dong JZ, Wang SL, Fan XW, Yang HT, Duan HY, Yan LJ, Qian P, Yang CK (2016) Advanced interatrial block predicts clinical recurrence of atrial fibrillation after catheter ablation. *J Cardiol* 68:352–356
- Park JK, Park J, Uhm JS, Joung B, Lee MH, Pak HN (2016) Low P-wave amplitude (<0.1 mV) in lead I is associated with displaced inter-atrial conduction and clinical recurrence of paroxysmal atrial fibrillation after radiofrequency catheter ablation. *Europace* 18:384–391
- Caldwell J, Koppikar S, Barake W, Redfearn D, Michael K, Simpson C, Hopman W, Baranchuk A (2014) Prolonged P-wave duration is associated with atrial fibrillation recurrence after successful pulmonary vein isolation for paroxysmal atrial fibrillation. *J Interv Card Electrophysiol* 39:131–138
- Okumura Y, Watanabe I, Ohkubo K, Ashino S, Kofune M, Hashimoto K, Shindo A, Sugimura H, Nakai T, Kasamaki Y, Saito S (2007) Prediction of the efficacy of pulmonary vein isolation for the treatment of atrial fibrillation by the signal-averaged P-wave duration. *Pacing Clin Electrophysiol* 30:304–313
- Kaypakli O, Koca H, Şahin DY, Okar S, Karataş F, Koç M (2018) Association of P wave duration index with atrial fibrillation recurrence after cryoballoon catheter ablation. *J Electrocardiol* 51:182–187
- Salah A, Zhou S, Liu Q, Yan H (2013) P wave indices to predict atrial fibrillation recurrences post pulmonary vein isolation. *Arq Bras Cardiol* 101:519–527
- Nakatani Y, Sakamoto T, Mizumaki K, Nishida K, Kataoka N, Tsujino Y, Yamaguchi Y, Inoue H (2016) Coefficient of variation of P-wave duration is a novel atrial heterogeneity index to predict recurrence of atrial fibrillation after catheter ablation. *J Cardiovasc Electrophysiol* 27:542–548
- Nogami A, Kurita T, Abe H, Ando K, Ishikawa T, Imai K, Usui A, Okishige K, Kusano K, Kumagai K, Goya M, Kobayashi Y, Shimizu A, Shimizu W, Shoda M, Sumitomo N, Seo Y, Takahashi A, Tada H, Naito S, Nakazato Y, Nishimura T, Nitta T, Niwano S, Hagiwara N, Murakawa Y, Yamane T, Aiba T, Inoue K, Iwasaki Y, Inden Y, Uno K, Ogano M, Kimura M, Sae S, Sasaki S, Satomi K, Shiga T, Suzuki T, Sekiguchi Y, Soejima K, Takagi M, Chinushi M, Nishi N, Noda T, Hachiya H, Mitsuno M, Mitsuhashi T, Miyauchi Y, Miyazaki A, Morimoto T, Yamasaki H, Aizawa Y, Ohe T, Kimura T, Tanemoto K, Tsutsui H, Mitamura H (2021) JCS/JHRS 2019 guideline on non-pharmacotherapy of cardiac arrhythmias. *J Arrhythm* 37:709–870
- Kanzaki Y, Inden Y, Ando M, Kamikubo Y, Ito T, Mizutani Y, Kato H, Fujii A, Yanagisawa S, Hirai M, Murohara T (2016) An ECG index of P-wave force predicts the recurrence of atrial fibrillation after pulmonary vein isolation. *Pacing Clin Electrophysiol* 39:1191–1197
- Doi A, Takagi M, Katayama H, Yoshiyama T, Hayashi Y, Tatsumi H, Yoshiyama M (2018) Diagnostic value of electrocardiographic P-wave characteristics in atrial fibrillation recurrence and tachycardia-induced cardiomyopathy after catheter ablation. *Heart Vessels* 33:1381–1389
- Kubala M, Lucena-Padros I, Xie S, Casado-Arroyo R, Frankel DS, Lin D, Santangeli P, Supple GE, Dixit S, Tschabrunn CM, Liang JJ, Yang J, Hyman MC, Zado ES, Marchlinski FE (2019) P-wave morphology and multipolar intracardiac atrial activation to facilitate nonpulmonary vein trigger localization. *J Cardiovasc Electrophysiol* 30:865–876

19. Kanemaru Y, Arima Y, Kaikita K, Kiyama T, Kaneko S, Ito M, Yamabe H, Motozato K, Yamanaga K, Fujisue K, Sueta D, Takashio S, Araki S, Usuku H, Nakamura T, Fukunaga T, Suzuki S, Izumiya Y, Sakamoto K, Soejima H, Yamamoto E, Kawano H, Kanazawa H, Tsujita K (2020) Elongation of the high right atrium to coronary sinus conduction time predicts the recurrence of atrial fibrillation after radiofrequency catheter ablation. *Int J Cardiol* 300:147–153
20. Yanagisawa S, Inden Y, Okamoto H, Fujii A, Sakamoto Y, Mamiya K, Tomomatsu T, Shibata R, Murohara T (2020) Electrocardiogram characteristics of P wave associated with successful pulmonary vein isolation in patients with paroxysmal atrial fibrillation: significance of changes in P-wave duration and notched P wave. *Ann Noninvasive Electrocardiol* 25:e12712
21. Ogawa M, Kumagai K, Vakulenko M, Yasuda T, Siegeman C, Garfinkel A, Chen PS, Saku K (2007) Reduction of P-wave duration and successful pulmonary vein isolation in patients with atrial fibrillation. *J Cardiovasc Electrophysiol* 18:931–938
22. Nakatani Y, Sakamoto T, Yamaguchi Y, Tsujino Y, Kataoka N, Kinugawa K (2020) P-wave vector magnitude predicts the left atrial low-voltage area in patients with paroxysmal atrial fibrillation. *J Electrocardiol* 59:35–40
23. Boriani G, Diemberger I, Biffi M, Camanini C, Valzania C, Corazza I, Martignani C, Zannoli R, Branzi A (2005) P wave dispersion and short-term vs. late atrial fibrillation recurrences after cardioversion. *Int J Cardiol* 101:355–361
24. Hazen MS, Marwick TH, Underwood DA (1991) Diagnostic accuracy of the resting electrocardiogram in detection and estimation of left atrial enlargement: an echocardiographic correlation in 551 patients. *Am Heart J* 122:823–828
25. Andlauer R, Seemann G, Baron L, Dossel O, Kohl P, Platonov P, Loewe A (2018) Influence of left atrial size on P-wave morphology: differential effects of dilation and hypertrophy. *Europace* 20:iii36–iii44
26. Kim DH, Kim GC, Kim SH, Yu HK, Choi WG, An IS, Kwan J, Park KS, Lee WH (2007) The relationship between the left atrial volume and the maximum P-wave and P-wave dispersion in patients with congestive heart failure. *Yonsei Med J* 48:810–817
27. Nattel S, Burstein B, Dobrev D (2008) Atrial remodeling and atrial fibrillation: mechanisms and implications. *Circ Arrhythm Electrophysiol* 1:62–73
28. Jadidi A, Muller-Edenborn B, Chen J, Keyl C, Weber R, Allgeier J, Moreno-Weidmann Z, Trenk D, Neumann FJ, Lehrmann H, Arentz T (2018) The duration of the amplified sinus-P-wave identifies presence of left atrial low voltage substrate and predicts outcome after pulmonary vein isolation in patients with persistent atrial fibrillation. *JACC Clin Electrophysiol* 4:531–543
29. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, Fetsch T, van Gelder IC, Haase D, Haegeli LM, Hamann F, Heidebüchel H, Hindricks G, Kautzner J, Kuck KH, Mont L, Ng GA, Rekosz J, Schoen N, Schotten U, Suling A, Taggeselle J, Themistoclakis S, Vettorazzi E, Vardas P, Wegscheider K, Willems S, Crijns H, Breithardt G (2020) Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 383:1305–1316
30. Potpara TS, Lip GYH, Blomstrom-Lundqvist C, Boriani G, Van Gelder IC, Heidebüchel H, Hindricks G, Camm AJ (2021) The 4S-AF scheme (stroke risk; symptoms; severity of burden; substrate): a novel approach to in-depth characterization (rather than classification) of atrial fibrillation. *Thromb Haemost* 121:270–278

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.