Original

New Parameter to Predict Recurrence of Paroxysmal Atrial Fibrillation after Pulmonary Vein Isolation by the P-Wave Signal-Averaged Electrocardiogram

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Abstract : Noninvasive methods for predicting the recurrence of atrial fibrillation (AF) after initial pulmonary vein isolation (PVI) have not been well described. The aim of the present study was to evaluate the usefulness of the P-wave signal-averaged electrocardiogram (P-SAECG) in predicting the recurrence of AF after initial PVI. The P-SAECG was recorded before and after (within 1 week) the initial PVI session. The filtered P-wave duration (FPD) and root mean square voltage of the last 20 ms of the filtered P-wave (LP20) were measured in 87 consecutive idiopathic AF patients (ejection fraction $\geq 50\%$, B-type natriuretic peptide $\leq 200\,\text{pg}\,/\,\text{ml}$). During the follow-up period (12 ± 7 months), 22 of 87 (25%) patients had recurrence of AF (11 with paroxysmal AF and 11 with persistent AF). In the group with recurrence of paroxysmal AF, the post-PVI FPD was significantly shorter and the post-PVI LP20 was significantly larger than in the non-recurrence group. Furthermore, the post-PVI LP20 / FPD ratio was significantly higher in the group with paroxysmal AF recurrence than in the non-recurrence group (0.024 ± 0.009 vs $0.015 \pm 0.007\,\mu\text{V}\,/\,\text{ms}$, respectively ; $P < 0.05$). Recurrence of paroxysmal AF was more frequently observed in patients with a post-PVI LP20 / FPD $> 0.015\,\mu\text{V}\,/\,\text{ms}$ than in those with a post-PVI LP20 / FPD $\leq 0.015\,\mu\text{V}\,/\,\text{ms}$. The optimal post-PVI LP20 / FPD cut-off value of $0.015\,\mu\text{V}\,/\,\text{ms}$ had a sensitivity of 90% and a specificity of 60%. The data also suggest that the post-PVI LP20 / FPD may be a new parameter for predicting successful PVI in patients with idiopathic paroxysmal AF after PVI.

Key words : P-wave signal-averaged electrocardiogram, late potential, atrial fibrillation, pulmonary vein isolation, recurrence

Introduction

Atrial fibrillation (AF) is the most frequently encountered arrhythmia in clinical practice, occurring in 1%–2% of the general population[1]. The pulmonary veins (PVs) play an important role in both the initiation and maintenance of AF[2, 3]. Recently, PV isolation (PVI) has been shown to be effective for curing paroxysmal and persistent AF[4, 5]. Furthermore, PVI for

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paroxysmal AF results in the maintenance of sinus rhythm (SR) without any antiarrhythmic drugs in 70%–90% of patients[6]. However, AF recurs in 10%–30% of patients after successful PVI. The recurrence rate is higher in patients with structural heart disease[7] or prolonged AF duration, such as persistent AF[8]. Persistent AF has been shown to lead to atrial interstitial fibrosis, resulting in an increased atrial conduction time[9]. This structural remodeling, in addition to electrophysiological remodeling such as a shortening or loss of the rate adaptation of the atrial refractory period[10] or prolonged atrial conduction times[11, 12], may increase the recurrence of AF after PVI. The signal-averaged electrocardiogram (SAECG) is a simple non-invasive method that has been used for years, initially to evaluate ventricular late potentials, but now is extended to the P-wave to provide a more accurate evaluation of atrial conduction. Many studies have used this method to evaluate reductions in P-wave duration to predict the recurrence of AF after PVI[13, 14]. In a previous report[14], patients with recurrence of AF after PVI, short filtered P-wave duration (FPD) and elevation of root mean square voltage of the last 20 ms of the filtered P-wave (LP20) are sometimes recorded. In these cases, the P-wave SAECG (P-SAECG) was recorded within 1 week after PVI; however, in a another previous report[13] the day of recording P-SAECG was not clear. Based on these observations, we thought that the FDP and LP20 within 1 week after PVI may be different from those reported in previous studies[13, 14]. Thus, the aim of the present study was to evaluate the usefulness of P-SAECG within 1 week after the initial PVI to establish a new parameter of the recurrence of AF after the initial PVI.

Materials and methods

Study population

The present study was a retrospective analysis of consecutive patients with AF. From April 2008 to November 2012, 87 consecutive patients [67 males, 20 females; mean (± SD) age 60 ± 12 years] who underwent an initial PVI session for paroxysmal (n＝65) or persistent (n＝22) AF in the Division of Cardiology, Department of Medicine, Showa University School of Medicine were evaluated. In the present study, paroxysmal AF was defined as AF terminating within 7 days, and persistent AF was defined as non-self-terminating AF lasting more than 7 days and requiring pharmacologic or electrical conversion to restore SR. Patients were excluded from the study if the P-SAECG was not properly recorded. Other exclusion criteria were as follows: structural heart disease, prior PVI, implanted pacemaker, mitral or aortic valve disease, left ventricular dysfunction [left ventricular ejection fraction (LVEF) ＜50%], and congestive heart failure [plasma B-type natriuretic peptide (BNP) concentrations ＞200 pg/ml]. P-SAECG was recorded before and after (within 1 week) the initial PVI in all patients.

Signal-averaged P-wave electrocardiography

Fig. 1 shows an example of a P-SAECG. This P-SAECG was recorded in the P-wave-triggered mode (FDX-6500; Fukuda Denshi Co., Tokyo, Japan). The P-wave signals (＞200 beats) were recorded from a standard 12-lead electrocardiogram (ECG) until the noise amplitude was
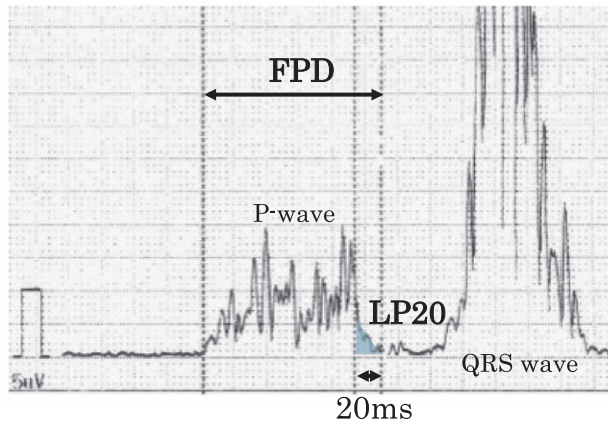
FPD：135ms
LP20：1.8μV
LP20/FPD = 1.8/135 (μV/ms)

Fig. 1. Sample P-wave signal-averaged electro-cardiogram (P-SAECG) trace. FPD, filtered P-wave duration; LP20, root mean square voltage of the last 20 ms of the filtered P-wave. Recordings were made using the FDX-6500 (Fukuda Denshi Co., Tokyo, Japan).

reduced to ＜0.4 μV. The signal from Lead II was filtered bidirectionally (with forward and backward filters) through a filter setting of 60 Hz, and a backward filter was used for the analysis in the present study. The filtered signals from Leads I, aVF, and V1 were combined into a vector magnitude of the P-wave. The FPD and LP20 were measured and the ratio LP20／FPD was calculated. Measurements of FPD and LP20 were made automatically and, if necessary, corrected manually by two physicians blinded to the clinical information of the patient.

Ablation procedure

A straight decapolar catheter was positioned in the high right atrium and coronary sinus. After trans-septal puncture at the fossa ovalis, the venous anatomy and location of the left atrial (LA)−PV junction were determined using a three-dimensional (3D) mapping system (CARTO, Biosence Webster Inc., Diamond Bar, CA, USA or NaVX, St. Jude Medical, St. Paul, MN, USA). Then, a circular catheter was placed first at the superior LA−PV junction and then at the contralateral LA−PV junction. The PVI was performed guided by the 3D mapping system. An irrigated ablation catheter was used for the mapping and ablation. Radiofrequency energy was applied for 15−30 s at each site using a maximum temperature of 40°C, maximum power of 35 W, and flow rate of 30 ml／min. An atrial circumferential ablation was performed to encircle the left- and right-sided PVs. The procedural endpoint was the electrical isolation of all PVs from the LA.

Follow-up

After the PVI session, patients were followed up for a period up to 2 years. The mean (±SD) follow-up period was 12±7 months. Oral anticoagulant drugs were continued in all patients and antiarrhythmic drugs were continued in 69 patients (79.3%). During the follow-up period, a surface 12-lead ECG was performed once a month and a 24-h ECG recording was performed at intervals of several months, as well as at any time that the patient had any

symptoms suggestive of AF, such as palpitations, dizziness, or syncope. The recurrence of AF was evaluated by 12-lead ECG recordings and a 24-h ECG recording. The blanking period was defined as the 3 months after PVI.

Statistical analysis

Patients were divided into three groups : a non-recurrence group (Non-Re), a group with recurrence of paroxysmal AF (Paroxy-Re) and a group with recurrence of persistent AF (Persis-Re). Comparisons were made between two groups, namely Non-Re vs. Paroxy-Re and Non-Re vs. Persis-Re, and the significance of differences in continuous variables was determined using Student's unpaired *t*-test, whereas the χ^2 or Fischer's exact test was used in comparisons of categorical data. To obtain an index of the overall FPD and RMS20 in the patients with and without recurrence of paroxysmal AF, a receiver operating characteristic (ROC) curve was generated and the area under the curve was calculated. The AF-free rates in the patients with an LP20 / FPD $\leqq 0.015\,\mu V$ / ms and $> 0.015\,\mu V$ / ms were calculated using the Kaplan-Meier method, and the difference between them was detected using the log-rank test. The duration of AF, left atrial dimension, LVEF, (of which the P values were less than 0.05 using the Student's *t*-test and χ^2 test) were evaluated by the Cox's multivariate regression analysis. Statistical significance was accepted at a $P < 0.05$. Where appropriate, data are given as the mean ± SD.

Results

Clinical characteristics

The clinical characteristics of patients in the Non-Re, Paroxy-Re, and Persis-Re groups are given in Table 1. There were no significant differences in the age, gender, duration of AF, LVEF, BNP, $CHADS_2$ score, or CHA_2DS_2-VASc score between the Non-Re and recurrence groups (Paroxy-Re or Persis-Re). The long axis of the left atrial diameter (LAD) was significantly longer in patients in the Persis-Re group compared to those in the Non-Re and Paroxy-RE groups (63.5 ± 10.7 vs. 53.4 ± 8.5 and 53.1 ± 10.3 mm, respectively ; $P < 0.05$).

Signal-averaged P-wave electrocardiography

There were no significant differences in FPD and LP20 before PVI between the Non-Re and Paroxy-Re or Persis-Re groups (pre-PVI FPD 134 ± 11.6 vs. 125 ± 11.5 and 149 ± 9.0 ms, respectively ; Fig. 2A). Conversely, the post-PVI FPD in the Paroxy-Re group was significantly shorter than in the Non-Re group (123 ± 9.1 vs. 131 ± 11.7 ms, respectively ; $P < 0.05$; Fig. 2B). The post-PVI LP20 in the Paroxy-Re group was significantly larger than in the Non-Re group (2.9 ± 1.1 vs. 2.0 ± 0.9 μV, respectively ; $P < 0.05$; Fig. 2B). There was no significant difference in the pre-PVI LP20 / FPD between the Non-Re and Paroxy-Re groups (0.018 ± 0.011 vs. 0.02 ± 0.007 μV / ms, respectively ; Fig. 3A), but there was a significant difference in the LP20 / FPD ratio between these two groups after the initial PVI (0.015 ± 0.007 vs. 0.024 ± 0.009 μV / ms, respectively ; $P < 0.05$; Fig. 3B).

Table 1.　Clinical characteristics of patients with non-recurrence and recurrence of paroxysmal or persistent atrial fibrillation（Paroxy-Re or Persis-Re, respectively）after initial pulmonary vein isolation

	Non-Re (n = 65)	Recurrence		P-value
		Paroxy-Re (n = 11)	Persis-Re (n = 11)	
Age（years）	61 ± 12	57 ± 12	57 ± 16	NS
No. men（%）	49（75.3%）	9（81%）	9（81%）	NS
Duration of AF（months）	53.0 ± 74*	54.9 ± 52	84.9 ± 55*	< 0.05
Echocardiography				
LAD long axis（mm）	53.4 ± 8.5*	53.1 ± 10.3[†]	63.5 ± 10.7*[†]	< 0.05
LAD short axis（mm）	41.7 ± 4.4	42.8 ± 4.9	44.9 ± 5.3	NS
LVEF（%）	62.9 ± 6.3*	61.9 ± 5.5	57.6 ± 5.6*	< 0.05
BNP（pg / ml）	51.3 ± 44	68.9 ± 52	68.6 ± 59	NS
Hypertension	33（50%）	7（63%）	7（63%）	NS
CHADS$_2$ score	0.8 ± 0.9	1.1 ± 0.7	1.0 ± 1.1	NS
CHA$_2$DS$_2$-VASc score	1.5 ± 1.3	1.7 ± 1.2	1.6 ± 1.5	NS
Persistent AF（%）	12（18.4%）*	3（27.2%）[†]	7（63.6%）*[†]	< 0.05

Data are presented as the mean ± SD or as n（%）. *$P < 0.05$ compared with Non-Re group and Persis-Re group ; [†]$P < 0.05$ compared with Paroxy-Re group and Persis-Re group. non-recurrence, Non-Re ; paroxysmal AF recurrence, Paroxy-Re ; Persistent recurrence AF, Persis-Re ; AF, atrial fibrillation ; LAD, left atrial diameter ; LVEF, left ventricular ejection fraction ; BNP, plasma B-type natriuretic peptide.

Predictors of AF recurrence

　To evaluate the total predictive performance of the post-PVI LP20, post-PVI FPD, and post-PVI LP20 / FPD for predicting Paroxy-Re, receiver operating characteristic（ROC）analyses were performed, revealing that the post-PVI LP20 / FPD was a more useful predictor of Paroxy-Re than either the post-PVI FPD or post-PVI LP20（Fig. 4A）. The optimal post-PVI LP20 / FPD cut-off value of 0.015 μV / ms had a sensitivity of 90% and a specificity of 60%. Fig. 4B shows the AF-free rate curve for patients with Non-Re（n = 65）or Paroxy-Re（n = 11）with a post-PVI Lp20 / FPD of ≤ 0.015 or ＞0.015 μV / ms. Paroxy-Re was more frequently observed in patients with a post-PVI LP20 / FPD ＞0.015 μV / ms than in those with a post-PVI LP20 / FPD ≤ 0.015 μV / ms（$P = 0.0027$, log-rank test）.

Clinical characteristics of patients with post-PVI LP20 / FPD ≤ 0.015 or ＞ 0.015 μV / ms

　The clinical characteristics of patients with a post-PVI LP20 / FPD ≤ 0.015 μV / ms（n = 41）or ＞0.015 μV / ms（n = 35）are given in Table 2. There were no significant differences in the age, gender, duration of AF, LVEF, BNP, CHADS$_2$ score, and CHA$_2$DS$_2$-VASc score between patients with a post-PVI LP20 / FPD of ≤ 0.015 and ＞0.015 μV / ms. However, hypertension was significantly more frequent in the group with post-PVI LP20 / FPD ＞0.015 μV / ms（n = 23）than in

A

Pre-PVI FPD

Pre-PVI LP20

B

Post-PVI FPD
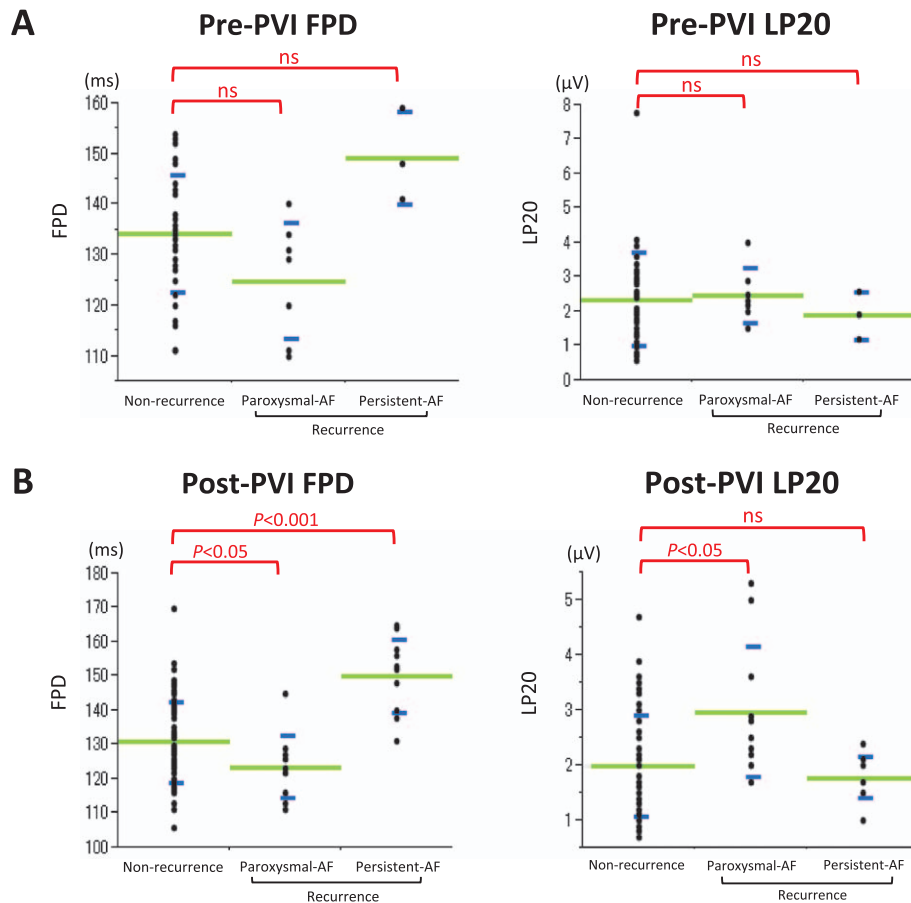

Post-PVI LP20

Fig. 2. Comparison of the filtered P-wave duration (FPD) and root mean square voltage of the last 20 ms of the filtered P-wave (LP20) before (A) and after (B) the initial pulmonary vein isolation (PVI) in patients without any recurrence (Non-Re) and in those with recurrence of paroxysmal or persistent atrial fibrillation (Paroxy-Re or Persis-Re, respectively). (A) There were no significant differences in the pre-PVI FPD and pre-PVI LP20 between the Non-Re and recurrence (Paroxy-Re or Persis-Re) groups. (B) The post-PVI FPD was significantly shorter in the Paroxy-Re than in the Non-Re group, whereas the post-PVI LP20 was significantly larger in the Paroxy-Re than in the Non-Re group. Green lines indicate the mean, with blue lines indicating the SD.

the group with post-PVI LP20 / FPD $\leq 0.015\,\mu$V / ms (n = 16; $P < 0.05$; Table 2).

Discussion

The present study is the first to describe the usefulness of the post-PVI LP20 / FPD for predicting Paroxy-Re after initial PVI. The main findings of the present study are the following: (i) the post-PVI FPD was significantly shorter and the post-PVI LP20 was significantly larger in the Paroxy-Re compared with the Non-Re group; and (ii) the post-PVI LP20 / FPD was useful for predicting Paroxy-Re after PVI, with a cut-off value of 0.015 μV / ms.

The findings in the present study of a significantly shorter post-PVI FPD and a significantly larger post-PVI LP20 in the Paroxy-Re versus Non-Re group are the opposite of those reported
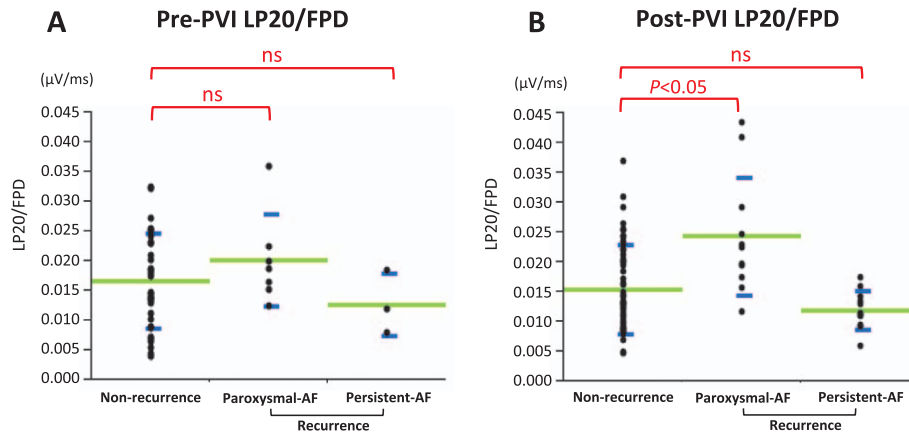
A — Pre-PVI LP20/FPD

B — Post-PVI LP20/FPD

Fig. 3. Ratio of the root mean square voltage of the last 20 ms of the filtered P-wave (LP20) to filtered P-wave duration (FPD) before (A) and after (B) the initial pulmonary vein isolation (PVI) in patients without any recurrence (Non-Re) and in those with recurrence of paroxysmal or persistent atrial fibrillation (Paroxy-Re or Persis-Re, respectively). (A) There were no significant differences in pre-PVI LP20/FPD between the Non-Re and Paroxy-Re or Persis-Re groups. (B) However, there was a significant difference in post-PVI LP20/FPD between the Non-Re and Paroxy-Re groups. Green lines indicate the mean, with blue lines indicating the SD.
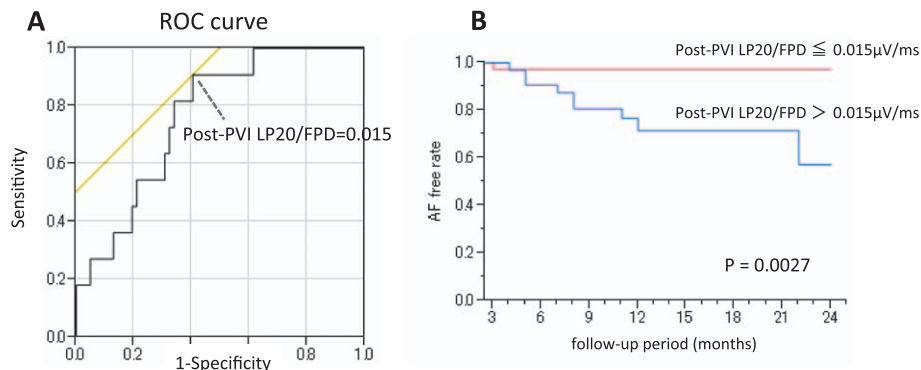
A — ROC curve

B

Fig. 4. (A) Receiver operating characteristic (ROC) curve for the various cut-off levels of the ratio of the root mean square voltage of the last 20 ms of the filtered P-wave (LP20) to filtered P-wave duration (FPD) after the initial pulmonary vein isolation (post-PVI) for predicting recurrence of atrial fibrillation (AF). (B) Kaplan−Meier curves for the survival-free rate from recurrence of paroxysmal AF in patients with a post-PVI LP20/FPD > 0.015 and ≤ 0.015 μV/ms. Patients with a post-PVI LP20/FPD > 0.015 μV/ms had a higher risk of recurrence of paroxysmal AF than those with a post-PVI LP20/FPD ≤ 0.015 μV/ms ($P = 0.027$, log-rank test).

previously. Previous studies[14, 15] reported that FPD is significantly reduced in patients without AF recurrence during the follow-up period. Okumura et al[15] measured SAECG before and after both ostial and circumferential PVI (CPVI; n = 51) in patients with paroxysmal and persistent AF. Patients with a successful outcome after CPVI had significant shortening of the FPD (from 146 ± 13 to 136 ± 12 ms; $P < 0.01$) compared with those in whom recurrence occurred

Table 2. Clinical characteristics of patients with values of ≤ 0.015 and ＞0.015 µV / ms for the ratio of the root mean square voltage of the last 20 ms of the filtered P-wave（LP20）/ filtered P-wave duration（FPD）after initial pulmonary vein isolation（post-PVI）

	Post-PVI LP20 / FPD		*P*-value
	≤ 0.015 µV / ms (n ＝ 41)	＞0.015 µV / ms (n ＝ 35)	
Age（years）	60.0 ± 13	61.7 ± 10	NS
No. men（%）	31（75.6%）	27（77.1%）	NS
Duration of AF（months）	63.8 ± 89	40.9 ± 39	NS
Echocardiography			
LAD long axis（mm）	53.4 ± 8.5	53.3 ± 9.0	NS
LAD short axis（mm）	41.5 ± 4.2	42.2 ± 4.8	NS
LVEF（%）	62.4 ± 6.5	63.1 ± 6.0	NS
BNP（pg / ml）	53.9 ± 43	53.6 ± 49	NS
Hypertension	17（41%）	23（65%）	＜0.05
CHADS$_2$ score	0.8 ± 0.8	1.0 ± 0.8	NS
CHA$_2$DS$_2$-VASc score	1.4 ± 1.2	1.6 ± 1.4	NS

Data are presented as the mean ± SD or as n（%）.
AF, atrial fibrillation ; LAD, left atrial diameter ; LVEF, left ventricular ejection fraction ; BNP, plasma B-type natriuretic peptide.

（from 167 ± 15 to 157 ± 15 ms ; P ＝ 0.2）. Furthermore, Ogawa *et al*[14] measured SAECG before and after segmental ostial catheter ablation（n ＝ 27）in patients with paroxysmal and persistent AF. Patients without AF recurrence during the follow-up period had a significant reduction in FPD（from 161 ± 7 to 151 ± 8 ms ; ΔFPD 10 ± 7 ms ; P ＜ 0.0001）, whereas there was no significant shortening in FPD in patients with AF recurrence（ΔFPD 2 ± 9 ms ; P ＝ NS）. A cut-off value of ≥ 5 ms for the reduction in the P-wave had a sensitivity of 92% and a specificity of 71% to predict a good clinical outcome. For that reason, shortening of the FPD after PVI was reported to be a predictor of successful AF ablation[16, 17]. In the present study, the results were the opposite of those reported in these previous studies. We suppose that the shortening of the FPD after PVI in the present study may be due to the complete electrical isolation of all four PVs at the time of the PVI session. However, during the follow-up period, there was a reconnection of the electrical conduction between the PV and LA in some patients. We suppose that consideration of other factors is necessary to predict the electrical reconnection of PVs.

The P-SAECG is useful for identifying individuals at risk of developing AF and those likely to change from paroxysmal to chronic AF[18]. Previous studies have shown that patients with chronic AF have a lower LP20 than those with paroxysmal AF[19]. However, the usefulness of the LP20 for the prediction of AF recurrence after PVI was not proven. Ogawa *et al*[14] performed computer simulation studies using a realistic 3D atrial activation model, and the results confirmed a reduction in P-wave duration and changes in the terminal portion of the P-wave morphology after simulated PVI. These findings suggest that the PV muscle sleeves are

responsible for the terminal portion of the P-wave, and they contribute to the late potentials on the P-SAECG. Furthermore, Ogawa *et al*[14] documented that the LP20 increased significantly after the PVI procedure, both in patients with either successful or failed ablation. Therefore, the LP20 was not proven as a useful parameter for prognostication after AF ablation. However, in the present study, in the case of only those patients with paroxysmal AF recurrence (the study population was limited to idiopathic AF patients with LVEF $\geq 50\%$ and BNP $\leq 200\,\mathrm{pg/ml}$), the post-PVI LP20 was significantly larger than in patients without recurrence, and these results proved that the LP20 was a useful parameter for the prediction of recurrence of paroxysmal AF after PVI.

The notable finding of the present study is that the shorter FPD and larger LP20 after initial PVI were significantly associated with a recurrence of paroxysmal AF, as indicated by univariate analysis, with multivariate analysis revealing that a post-PVI LP20/FPD $> 0.015\,\mathrm{\mu V/ms}$ was a predictor of the recurrence of paroxysmal AF. However, post-PVI LP20/FPD is not a useful predictor of the recurrence of persistent AF. We believe that the likely explanation for this finding is related to the different mechanisms of initiation and maintenance of AF. Activity triggered from the LA−PV junction initiates AF and causes paroxysmal AF. Atrial structural remodeling, in addition to electrophysiological remodeling, is responsible for the maintenance of AF, and causes paroxysmal AF. Modifications in FPD and LP20 after PVI reflect the electrical isolation of the LA−PV junction. For this reason, the post-PVI FDP and LP20 are not associated with the recurrence of persistent AF.

Study limitations

The present study has several limitations. First, measurement of the P-SAECG is sometimes difficult because of noise, inappropriate cardiac rhythms, or overlap between the end of the P-wave and the beginning of the QRS complex. Our definition of atrial late potentials was arbitrary because there are no established criteria for atrial late potentials. In addition, pre-ablation antiarrhythmic drug therapy was not discontinued and the treatment was maintained after the procedure ; some drugs may have affected FPD. Furthermore, asymptomatic recurrence may have occurred during the follow-up period and the rate of recurrence may have been underestimated. Such limitations are also applicable to all studies of PVI for AF. Further prospective studies are needed to ascertain the relationship between AF recurrence and LP20/FPD.

Conclusions

The post-PVI LP20/FPD may be useful for predicting paroxysmal AF recurrence in patients with idiopathic AF after PVI.

Conflict of interest disclosure

The authors have declared no conflict of interest.

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