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ORIGINAL ARTICLE

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Notched P-wave on digital electrocardiogram predicts the recurrence of atrial fibrillation in patients who have undergone catheter ablation

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Abstract

Background: A notched P-wave is associated with the occurrence of atrial fibrillation (AF). However, the association between a notched P-wave and AF recurrence in patients who have undergone a catheter ablation for AF is unclear.

Methods: We enrolled 100 subjects who underwent catheter ablation for AF (paroxysmal AF: 60 cases; persistent AF: 40 cases). Twelve-lead electrocardiography (ECG) was conducted, and the peak-to-peak distance in the M shape was calculated automatically using a 12-lead ECG analysis system. A notched P-wave was defined as a P-wave with an M-shape and a peak-to-peak distance of ≥20 ms in lead II. We compared the recurrence of AF in the patients with notched P-wave and the others.

Results: The mean follow-up period was 12 ± 8 months, and a recurrence of AF was observed in 28 patients. The recurrence of AF in the notched P-wave group was significantly higher than that in the controls (log rank 5.14, $p = .023$). A notched P-wave was a significant predictor of the recurrence of AF after adjustment for age, gender, history of heart failure, history of catheter ablation, persistent AF, use of antiarrhythmic drugs, and the left atrial volume index (hazard ratio 2.470, 95% confidence interval 1.065–5.728, $p = .035$).

Conclusions: Automatically identified notched P-waves with peak-to-peak distance ≥20 ms were associated with AF recurrence in patients who had undergone catheter ablation.

KEYWORDS
atrial fibrillation, catheter ablation, electrocardiogram, P wave, prognosis

1 | INTRODUCTION

The P-wave on 12-lead electrocardiogram (ECG) represents atrial activation (depolarization), and atrial remodeling causes intra/interatrial conduction delay, resulting in P-wave morphological changes.[1]

The latter part of the P-wave represents left atrial activation. The morphological change of the mitral P-wave seen in lead II on a 12-lead ECG is recorded as the notched P-wave and reflects conduction delay caused by left atrial loading/remodeling.[2,3] Morphological changes in the P-wave and notched P-wave have been reported to be associated with the development of stroke and atrial fibrillation,[4,5] and a notched P-wave in the 12-lead ECG has been shown to predict recurrence of atrial fibrillation (AF) in patients who have undergone catheter ablation.[6]

Previous reports have focused on the notched P-wave as measured visually on the ECG, but recent reports have also revealed an association between the automatically assessed notched P-wave and cardiovascular events.[7] However, the association between the automatically assessed notched P-wave and recurrence of AF in patients who have undergone catheter ablation is unclear. The aim of this study was to investigate the association between the automatically assessed notched P-waves on digital ECG and recurrence of AF in patients who have undergone catheter ablation.

2 | METHODS

2.1 | Subjects

We enrolled patients who underwent catheter ablation at our institution ($N=167$) from the Coupling and Coupling ONE studies (Figure S1). We analyzed patients ($N=100$; paroxysmal AF: 60 cases; persistent AF: 40 cases) after the exclusion of those whose ECGs could not be analyzed automatically ($N=67$). The study period was from July 2016 to December 2019. Details of this study are reported elsewhere.[8,9] This study was conducted by only our hospital. The coupling and coupling ONE studies are prospective observational evaluations of the suitability of CAVI values for predicting cardiovascular events in Japanese patients who had one or more of the following risk factors: atrial fibrillation, hypertension, smoking, kidney disease, and/or history of cardiovascular disease (coronary artery disease, stroke, aortic dissection, or hospitalization for heart failure).[8,9] The Ethics Committee of the Internal Review Board of the Jichi Medical University School of Medicine approved both protocols. Written informed consent was obtained from all patients who were enrolled in the study. Informed consent was obtained from all patients.

2.2 | ECG analysis

The ECG analysis was performed during sinus rhythm the day after the ablation procedure. Details of this ECG analysis were reported elsewhere.[1,7] The digital 12-lead electrocardiography were recorded at a sampling rate of 500 Hz and 4.88 μV resolution over 10 s, and the parameters in the P wave in lead II were calculated by averaging the ECGs. The peak-to-peak distance in the M shape in lead II was calculated and stored automatically using a 12-lead ECG analysis system (CardiMax series; Fukuda Denshi, Tokyo). Notched P-waves in lead II on ECG were evaluated and classified as M-shaped or not M-shaped (Figure 1). (1) A valley was found in the section from the start point to the end point of the P-wave in the averaged waveform of lead II. (2) The maximum value A between the start point of the P-wave and the valley was identified. (3) The maximum value B between the valley and the end point of the P-wave was identified. (4) The notch interval was defined by the distance between A and B. The P-wave was defined as notched when it had an M-shape with a peak-to-peak distance of ≥20 ms (half of the smallest unit on paper ECG recordings) in lead II.[7] The peak-to-peak distance in the M shape in lead II was calculated and stored automatically using a 12-lead ECG analysis system. The accuracy of the automatic 12-lead ECG analysis system and visual analysis on paper 12-lead ECG has been demonstrated previously.[7] No patient had a negative p-wave in lead II in this study.

We also recorded the width of the P wave in lead II by automatic analysis and divided the patients into two groups at 108 ms based on previous reports.[10]

2.3 | Echocardiography

Echocardiography was performed during sinus rhythm or atrial fibrillation before the ablation procedure. Two-dimensional M-mode or B-mode echocardiography were performed according to the guidelines of the American Society of Echocardiography (ASE) and the European Society of Echocardiography.[11] The left atrial volume (LAV) measurements were calculated using the biplane area-length method according to the guidelines of the ASE.[11] Two-dimensional volumetric measurements were based on left atrial area measurement by tracing the blood–tissue interface and left atrial length on apical four-lumen and two-lumen views. The left atrial volume index (LAVI) was defined as the left atrial volume indexed for body surface area. The left atrial volume index (LAVI) was calculated by correcting the mean left atrial volume (LAV) by body surface area.

2.4 | Ablation procedure

The indications for ablation conformed to Class I-IIb of the JCS/JHRS guideline.[12] Age, left atrial size, and duration were not included in the exclusion criteria. Details of ablation procedure and follow-up are reported elsewhere.[13] All antiarrhythmic drugs were discontinued for at least five half-lives before the procedure. The procedure was performed under moderate sedation by dexmedetomidine and fentanyl. If the AF persisted at the beginning of the procedure, internal cardioversion under deep sedation by thiopental was performed before catheter ablation. The catheter ablation was performed using an irrigated-tip contact force-sensing catheter through a deflectable sheath in all cases guided by the three-dimensional mapping system. If the patients had clinically documented typical atrial flutter, a cavotricuspid isthmus block line was created.[13]

2.5 | Follow-up

We observed continuous, in-hospital ECG monitoring for 2–3 days after the procedure. The first outpatient clinic visit was 3 weeks after the procedure. All patients were followed-up by a clinical interview, ECGs every 3 months, and 24-h Holter monitoring every 3–6 months at our clinic to evaluate AF recurrence. Patients with palpitations were encouraged to visit our hospital.[13]

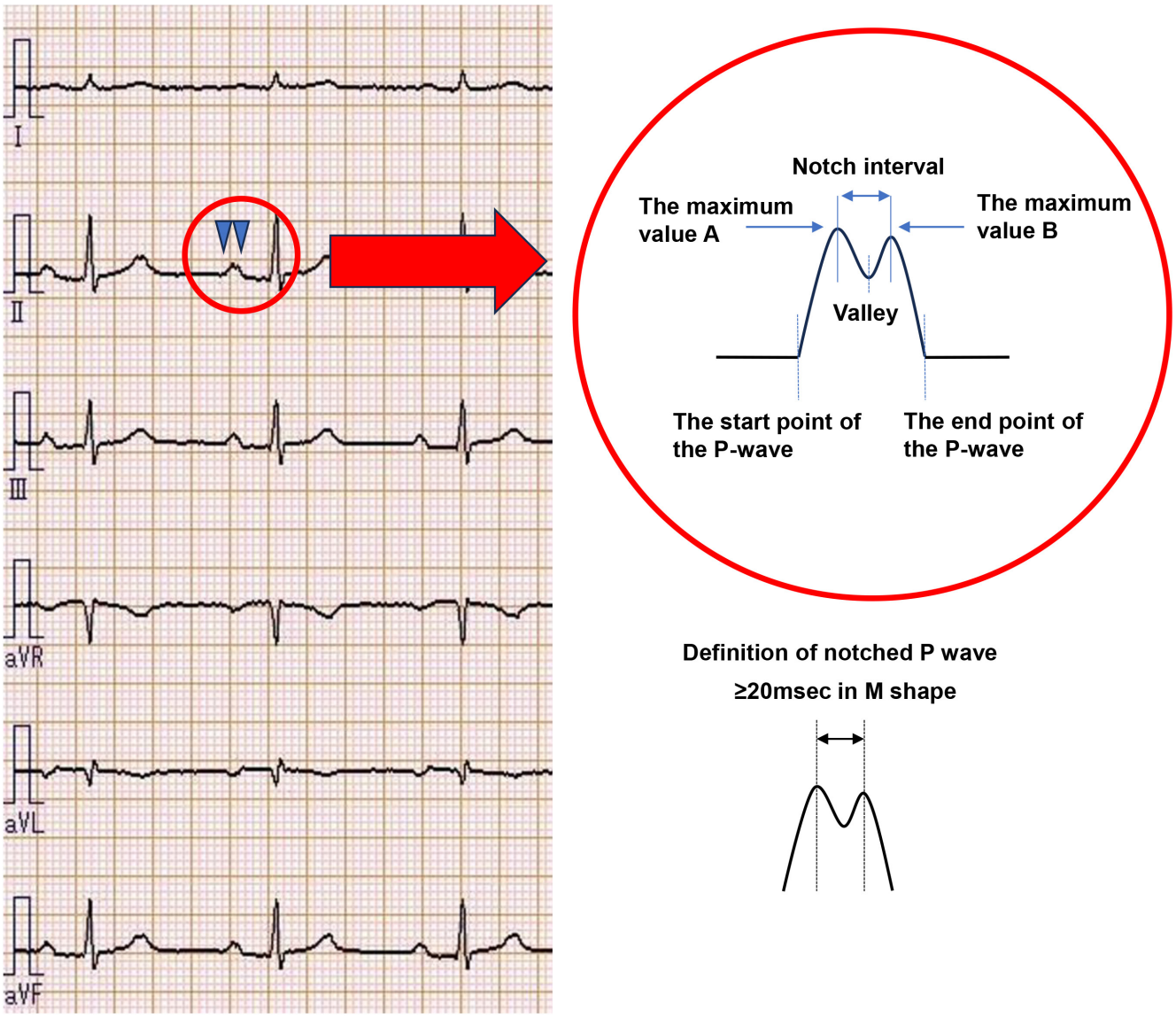

FIGURE 1 The measurements of notch interval and definition of a notched P-wave.

2.6 | Endpoints

The primary endpoint was defined as recurrence of AF after catheter ablation. The first 3 months after catheter ablation was defined as a blanking period. Recurrence of AF was defined as AF or atrial tachycardia sustained for more than 30 s on 12-lead ECG or Holter ECG after a blanking period.[14]

2.7 | Statistical analysis

Data are presented as the means ± standard deviations for normally distributed variables or as the median [25th, 75th percentiles] for non-normally distributed variables or a percentage. Consecutive data from the two study groups were analyzed using Student's *t*-test. The χ^2 test was used for the categorical data. The Kaplan–Meier curves of the cumulative incidence of recurrence of AF after catheter ablation in the group with a notched P-wave and that without a notched P-wave were calculated, and the differences in the rate of events between the two groups were assessed by the log-rank test.

In addition, we examined the relationship between a notched P-wave and AF recurrence after ablation in the groups with paroxysmal AF and persistent AF using the Kaplan–Meier curve. Hazard ratios and 95% confidence intervals for the notched P-wave and control groups for the primary endpoint after adjustment for age, gender, hypertension, diabetes mellitus, history of heart failure, history of catheter ablation, use of antiarrhythmic drugs, persistent AF, and LAVI were evaluated using a Cox proportional hazard model. All statistical analyses were performed using SPSS version 26.0 software (IBM, Chicago, IL, USA); *p*-values <.05 were considered statistically significant.

3 | RESULTS

The average age of patients in this study was 60.9 ± 10.8 years, and the percentage of male subjects was 74%. The number of patients categorized into the notched P-wave group was 26 (26%).

The baseline patient characteristics in the notched P-wave and control groups are shown in Table 1. The population included 12 patients (12%) with a history of catheter ablation; antiarrhythmic drugs were taken in 54 patients (54%). Although there was no significant difference in the duration of AF or the use of antiarrhythmic drugs between the notched P-wave group and the controls, the percentage of history of catheter ablation was significantly higher in the notched P-wave group (27% vs. 8%, $p = .036$). The heart rate at the time of ECG measurement was significantly higher in the notched P-wave group compared to the control group (74.3 ± 17.4 vs. 64.3 ± 19.3 bpm; $p = .039$). There were no significant differences in echocardiographic results such as LAVI and LVMI between the notched P-wave group and the controls (Table 1).

The mean follow-up period was 12 ± 8 months, and a recurrence of AF was observed in 26 patients. Figure 2 shows the Kaplan–Meier curve for AF recurrence. The incidence of AF recurrence was significantly higher in the notched P-wave group compared to the control group (log rank 5.14, $p = .023$; Figure 2). Categorization into the notched P-wave group was a significant predictor of the recurrence of AF after adjustment for age, gender, history of heart failure, history of catheter ablation, use of antiarrhythmic drugs, and LAVI (hazard ratio 2.470, 95% confidence interval 1.065–5.728, $p = .035$; Table 2).

We evaluated the association between notched P and AF recurrence in patients with paroxysmal AF and persistent AF separately. In both groups, the incidence of AF recurrence tended to be higher in the group with notched P waves, but the difference was not significant (paroxysmal AF: log rank 1.488, $p = .223$; persistent AF: log rank 3.539, $p = .060$; Figure 3). In addition, no significant difference was observed in the Cox proportional hazards model after adjustment for age, gender, history of heart failure, history of catheter ablation, use of antiarrhythmic drugs, and LAVI (Table 3).

Finally, we assessed the incidence of AF recurrence according to P wave duration (<108 vs. ≥108 ms) in our study patients. The incidence of AF recurrence in patients with P wave duration ≥108 ms was not significantly different compared to that in patients with P wave duration <108 ms (log rank 0.139, $p = .709$; Figure 4). Furthermore, Cox proportional hazards models after adjustment for age, gender, hypertension, diabetes, history of heart failure, antiarrhythmic drugs, persistent AF, and LAVI revealed that P wave duration ≥108 ms was not an independent predictor of AF recurrence (Table 4).

4 | DISCUSSION

In the present study, the notched P-wave with a peak-to-peak distance of ≥20 ms was significantly associated with the recurrence of AF in patients having at least one cardiovascular risk factor who had undergone catheter ablation. The risk of recurrence of AF in subjects

TABLE 1 Comparison of clinical and procedural characteristics between patients with and without notched P-wave.

	Without notched P-wave ($N = 74$)	With notched P-wave ($N = 26$)	*p* value
Age (year)	61 ± 11	60 ± 10	.549
Male (%)	72	81	.340
Body mass index (kg/m^2)	24.9 ± 4.0	23.3 ± 3.6	.065
Persistent AF (%)	36	50	.230
Duration of AF (months)	10.0 [5.0–43.0]	24.5 [8.5–60.0]	.387
History of stroke (%)	8	8	.953
History of heart failure (%)	5	0	.045
Current smoker (%)	5	8	.676
Antiarrhythmic drugs (%)	53	58	.664
History of catheter ablation (%)	8	27	.036
Hypertension (%)	66	54	.266
Diabetes mellitus (%)	9	15	.411
Dyslipidemia (%)	41	35	.599
Heart rate at the time of ECG (bpm)	64.3 ± 19.3	74.3 ± 17.4	.039
Left atrial diameter (mm)	40.7 ± 6.0	40.1 ± 6.8	.597
LAVI (mL/m^2) ($N = 85$)	42.1 ± 13.8	40.1 ± 14.9	.554
Left ventricular mass index (g/m^2) ($N = 85$)	93.5 ± 26	90.2 ± 18.7	.576
Left ventricular ejection fraction (%) ($N = 85$)	62.3 ± 9.7	64.6 ± 9.2	.301

Abbreviations: AF, atrial fibrillation; ECG, electrocardiography; LAVI, left atrial volume index.

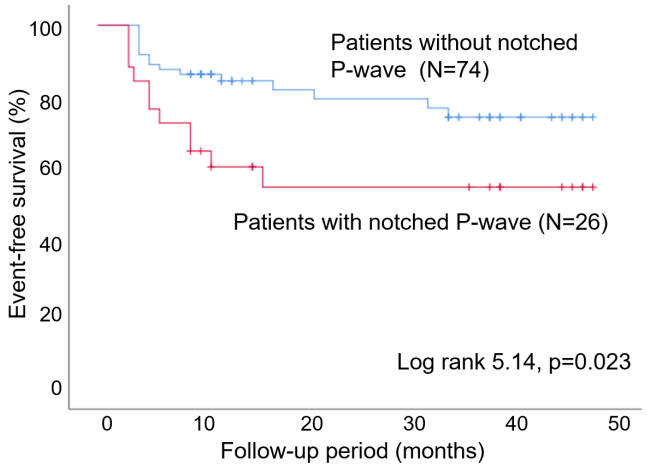

FIGURE 2 Event-free survival in patients with and without notched P-waves.

TABLE 2 Cox proportional hazards model of the recurrence of AF.

	Hazard ratio (95% CI)	*p* value
Notched P	2.470 (1.065–5.728)	.035
Age (per 1 year)	0.989 (0.944–1.035)	.624
Gender (female)	0.383 (0.153–0.960)	.041
LAVI (per mL/m^2)	1.023 (0.994–1.052)	.118
History of heart failure	1.146 (0.134–9.768)	.901
Hypertension	0.486 (0.201–1.175)	.109
Diabetes mellitus	0.837 (0.181–3.873)	.819
Antiarrhythmic drugs	1.555 (0.634–3.815)	.335
History of catheter ablation	2.329 (0.799–6.794)	.122
Persistent AF	1.007 (0.435–2.333)	.986

Abbreviations: AF, atrial fibrillation; CI, confidence interval; LAVI, left atrial volume index.

with a notched P-wave was more than twice that of subjects without a notched P-wave.

The morphology of the P-wave on the ECG is defined by the activation patterns of the left and right atrium. The latter part of the P-wave represents left atrial activation, and the morphological change of the mitral P-wave seen in lead II on a 12-lead ECG is recorded as the notched P-wave and reflects the conduction delay caused by left atrial loading/remodeling.[2,3]

We previously showed that manually measured notched P-waves with a peak-to-peak distance of 40 ms were associated with cardiovascular events,[5] and automatic measurement has since achieved the identification of notched P-waves with half that peak-to-distance, suggesting that notched P-waves with peak-to-peak distances of ≥20 ms are associated with cardiovascular events.[7] Dilaveris et al. reported that manual P-wave analysis on ECG at standard paper speed has limited measurement accuracy.[15] Automatic analysis of notched P-waves would be useful to obtain more accurate measurements, based on the previous finding that an automatically identified notched P-wave with a peak-to-peak distance of 20 ms was associated with a significant difference in the recurrence of AF in patients who had undergone catheter ablation, which was replicated in our present study.

In this study, multivariate analysis revealed that LAVI was not a significant predictor of recurrence, while notched P-wave was a significant factor. Electrical remodeling may precede morphological changes in the left atrium in hypertensive patients.[16] That is, a notched P-wave may precede left atrial enlargement on echocardiography. In the absence of left atrial enlargement, a notched P-wave may reflect atrial remodeling and be predictive of the prevention of AF recurrence in post-ablation patients. Intra-atrial conduction delay from electrical remodeling plays an important role in the onset and maintenance of AF.[17,18] Accordingly, a future study will be needed to investigate whether notched P-waves are associated with AF recurrence after ablation in a larger population

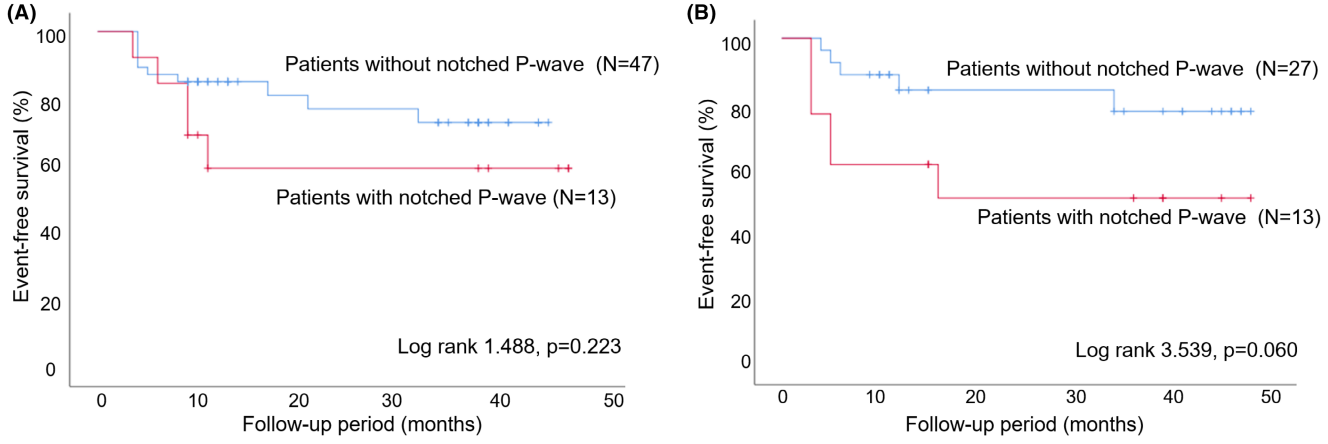

FIGURE 3 Event-free survival in patients with and without notched P-waves. (A) The patients with paroxysmal AF. (B) The patients with persistent AF. AF, atrial fibrillation.

TABLE 3 Cox proportional hazards model for AF recurrence assessed with patterns of Clinical Presentation of AF.

	Paroxysmal AF		Persistent AF	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Notched P	2.084 (0.583–7.455)	.259	4.757 (0.976–23.19)	.054

Abbreviations: AF, atrial fibrillation; CI, confidence interval.

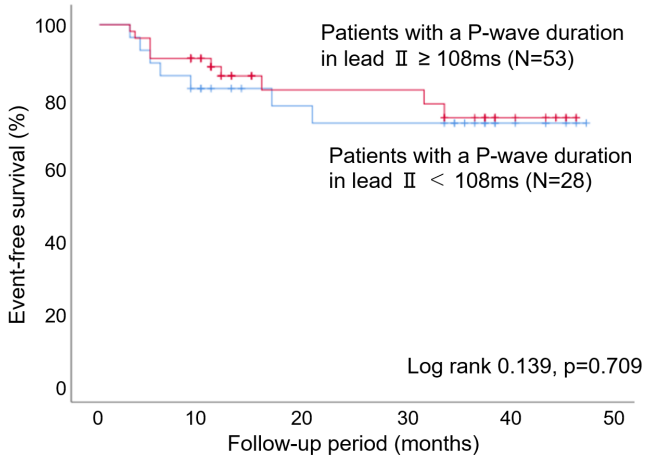

FIGURE 4 Event-free survival in patients with and without a P-wave duration in lead II of ≥108 ms.

TABLE 4 Cox proportional hazards model for AF recurrence (P-wave duration in lead II ≥108 ms).

	Hazard ratio (95% CI)	*p* value
P wave duration in lead II ≥108 ms	0.459 (0.176–1.197)	.111
Age (per 1 year)	0.993 (0.949–1.040)	.769
Gender (female)	0.428 (0.175–1.049)	.064
LAVI (per mL/m^2)	1.019 (0.989–1.050)	.225
History of heart failure	0.896 (0.102–7.873)	.921
Hypertension	0.430 (0.169–1.093)	.076
Diabetes mellitus	1.012 (0.220–4.656)	.987
Antiarrhythmic drugs	1.742 (0.690–4.401)	.240
History of catheter ablation	2.123 (0.713–6.325)	.176
Persistent AF	0.903 (0.364–2.244)	.827

Abbreviations: AF, atrial fibrillation; CI, confidence interval; LAVI, left atrial volume index.

without left atrial enlargement. Other analysis has already shown that the dispersion and late potential of P-waves are related to AF onset and the recurrence of AF in patients who have undergone catheter ablation.[19] Continued elucidation of the significance of AF-related P-waves is expected. In this study, neither persistent AF nor LAVI was found to confer a significant risk of AF recurrence. We speculated that the lack of significant difference in AF recurrence between patients with and without persistent atrial fibrillation or LAVI was because of collinearity.

The 20 msec notch that was found to be significant in this study is half of the minimum box in the ECG. Therefore, we consider that the risk of recurrence of AF can be assessed if the notch is more than half of the minimum box, even if it is visually observed.

The main limitations of this study were the short follow-up period and the small number of subjects. Larger-scale, longer-term studies are needed in the future. The small number of patients in this study was partly because of the use of a special electrocardiograph, and in the future, it will be necessary to examine whether this device can be applied in conjunction with a general ECG system. The notched P-wave was dynamically changed after AF catheter ablation (delayed or diminished), which was also reported in a previous study.[6] However, the present study included a large number of patients with persistent atrial fibrillation, and the ECG before catheter ablation was not compatible with automated analysis, making it difficult to assess P wave changes over time before and after ablation.

5 | CONCLUSIONS

The automatically assessed notched P-wave defined by a peak-to-peak distance of ≥20 ms was associated with the recurrence of AF in patients who had undergone catheter ablation.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

TK reports research and education support from Medtronic, Japan Lifeline, and Abbott. KK reports lecture fees from Omron Healthcare and A&D; funded research or joint research expenses from Omron Healthcare and Fukuda Denshi outside the submitted work.

DATA AVAILABILITY STATEMENT

The data of this study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL STATEMENT

The ethics committee of the internal review board of the Jichi Medical University School of Medicine approved the protocol (A14-184 and A17-130).

PATIENT CONSENT STATEMENT

Informed consent was obtained from all patients.

CLINICAL TRIAL REGISTRATION

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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