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Coefficient of variation of P-wave duration measured using an automated measurement system predicts recurrence of atrial fibrillation

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ABSTRACT

Background: P-wave parameters representing atrial conduction heterogeneity are associated with recurrence of atrial fibrillation (AF) after catheter ablation. However, intra- and inter-observer variabilities are unavoidable during manual measurement of P-wave parameters.

Methods: The study included 201 patients with paroxysmal AF who underwent catheter ablation. P-wave duration (PWD) was measured using a computerized automated measurement system with a surface 12-lead electrocardiogram. The coefficient of variation of PWD (CV-PWD) across the 12 electrocardiographic leads was determined as an index of atrial conduction heterogeneity.

Results: AF did not recur in 157 (78%) patients during a 12-month follow-up period. CV-PWD assessed before catheter ablation was not different between the AF-recurrent and AF-free groups (0.069 ± 0.023 vs. 0.069 ± 0.023, $P = 0.090$). However, CV-PWD measured after catheter ablation was significantly larger in the AF-recurrent group than in the AF-free group (0.090 ± 0.037 vs. 0.073 ± 0.024, $P < 0.001$). In receiver operating curve analysis, CV-PWD assessed after catheter ablation achieved an area under the curve of 0.702; the sensitivity, specificity, and positive and negative predictive values were 68%, 69%, 38%, and 88%, respectively, for the cut-off value of 0.080. During the follow-up period, AF freedom rates of high CV-PWD patients (CV-PWD ≥ 0.080) and low CV-PWD patients (CV-PWD < 0.080) were 65% and 88%, respectively.

Conclusions: CV-PWD determined using an automated measurement system was associated with AF recurrence after catheter ablation in patients with paroxysmal AF.

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Introduction

Catheter ablation has evolved as one of the primary treatment options for atrial fibrillation (AF) after the pulmonary veins were identified as an essential trigger of AF [1]. Recent technological advancements have enhanced the efficacy of catheter ablation for AF; however, recurrence of AF in patients who undergo catheter ablation is high. Therefore, prediction of AF recurrence after catheter ablation is crucial for determining appropriate treatment strategies.

Several characteristic atrial changes are typically observed in patients suffering from AF. These include loss of atrial myocardium, interstitial fibrosis, and alterations in the expression of ion channels [2,3]. Furthermore, these histological and functional changes in the atria lead to atrial conduction heterogeneity [3–5], which is one of the most critical factors in the pathogenesis of AF. Therefore, electrocardiographic parameters, which represent atrial conduction heterogeneity, are associated with the development of AF. For instance, P-wave dispersion, calculated by subtracting the minimum P-wave duration (PWD) from the maximum PWD as measured by a surface 12-lead electrocardiogram (ECG), was associated with AF occurrence [6,7] and recurrence after cardioversion [8] and catheter ablation [9]. Furthermore, the coefficient of variation of PWD (CV-PWD) across the 12 electrocardiographic leads, which we previously devised as an index of atrial conduction heterogeneity, showed a high diagnostic accuracy for predicting AF recurrence after catheter ablation [10].

Previous studies have manually measured PWD [6–10]; thus, intra- and inter-observer variabilities were unavoidable. Moreover, due to the time-consuming and labor-intensive nature of manual measurements of PWD, clinical applications are challenging. Therefore, in the present study, we determined PWD using a computerized automated measurement system and assessed the relationship between P-wave parameters, representing atrial conduction heterogeneity, and AF recurrence after catheter ablation.

Material and methods

Study population

In this study, we retrospectively enrolled consecutive 201 patients with paroxysmal AF who underwent catheter ablation at the Toyama

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University Hospital (Toyama, Japan) from January 2010 to December 2016. Paroxysmal AF was defined as AF lasting <7 days [11]. We excluded patients with previous catheter ablation, prior heart surgery, thyroid disease, pulmonary disease, as well as those administered anti-arrhythmic drugs after catheter ablation. Clinical characteristics, including comorbidities, echocardiographic data, and laboratory data, were obtained from medical records. This study's protocol was approved by the Institutional Research and Ethics Committee of the University of Toyama (Toyama, Japan) and was conducted in accordance with the principles of the Declaration of Helsinki. Furthermore, we obtained written informed consent from patients before ablation.

Assessment of surface 12-lead ECG

The standard 12-lead ECG was assessed immediately before ablation and one day following the procedure. All anti-arrhythmic drugs were discontinued for at least five half-lives, and no patients received oral amiodarone before ablation. Moreover, anti-arrhythmic drugs were not resumed after ablation. Therefore, all ECGs were recorded without the influence of anti-arrhythmic drugs. ECG was recorded with a paper speed of 25 mm/s and a gain setting of 0.1 mV/mm using a digital ECG (Fukuda Denshi, Tokyo, Japan). PWD was automatically measured using a computerized automated measurement system (Fukuda Denshi). Detection of the P wave was performed from the onset point of the QRS complex toward the offset point of the preceding T wave. The detection level of the P wave was determined with reference to the noise level of the baseline portion. The offset point of the P wave was defined as the point where the amplitude of potential first exceeded the detection level, whereas the onset point was defined as the point where the amplitude of potential fell below the detection level. Furthermore, the onset point of the P wave was re-examined in the opposite direction. PWD was determined as the time interval between the onset and offset points of the P wave.

P-wave dispersion was calculated by subtracting the minimum PWD from the maximum PWD recorded in the surface 12-lead ECG [6–9]. CV-PWD was calculated by dividing the standard deviation of PWD by the mean value of PWD [10]. Representative cases of the determination of P-wave dispersion and CV-PWD are shown in Fig. 1. The association of maximum PWD, P-wave dispersion, and CV-PWD with AF recurrence after ablation was assessed.

Catheter ablation

The NavX system (St. Jude Medical Inc., St. Paul, MN, USA) was used for three-dimensional (3D) mapping. Sheath introducers were inserted through the right femoral vein of patients under sedation. A 5-F deflectable catheter was inserted into the coronary sinus. The trans-septal procedure was performed using fluoroscopic landmarks, and three 8-F SL0 sheaths (St. Jude Medical, Inc.) were advanced into the left atrium. The 3D geometry was created on the NavX system, and sequential contact mapping was performed using a 7-F decapolar circular catheter (Lasso, Biosense-Webster, Inc., Diamond Bar, CA, USA; Libero, Japan Lifeline Co., Ltd., Tokyo, Japan). Pulmonary vein isolation was performed under the guidance of 3D mapping and two 7-F decapolar circular catheters (Lasso or Libero) positioned at the ipsilateral pulmonary vein ostia. At the anterior aspect of the left pulmonary veins, an ablation line was created along the ridge between the left atrial appendage and pulmonary vein ostium. Each radiofrequency application was delivered for

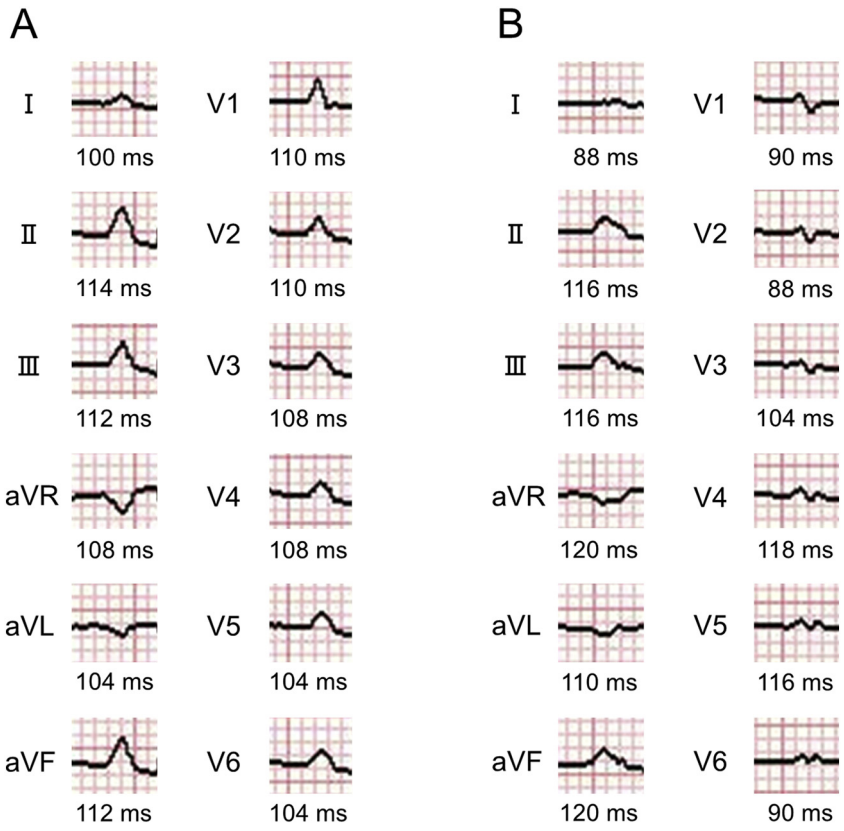

Fig. 1. Representative measurements of P-wave parameters. A) A 48-year-old female patient with no AF recurrence after ablation. The maximum P-wave duration (PWD) and minimum PWD were 114 ms in lead II and 100 ms in lead I, respectively. P-wave dispersion was calculated as 14 ms. The standard deviation and mean value of PWD were 4 ms and 108 ms, respectively. The coefficient of variation of PWD (CV-PWD) was calculated as 0.037. B) A 65-year-old male patient with AF recurrence after ablation. The maximum PWD, P-wave dispersion, and CV-PWD were 120 ms, 32 ms, and 0.127, respectively.

30–50 s. An irrigated tip radiofrequency catheter (Safire BLU or FlexAbility, St. Jude Medical Inc.) was used with a maximum temperature and power of 42 °C and 30 W, respectively. A maximum power of 25 W was used while delivering energy to sites near the esophagus. An entrance block was confirmed by elimination or dissociation of pulmonary vein potentials recorded at the circular catheters placed within the pulmonary veins, and an exit block was confirmed by pacing from these circular catheters. The procedure was completed after creating a block line on the cavotricuspid isthmus.

Post-procedure care and follow-up

A clinical interview and a surface 12-lead ECG were performed on the day following ablation and at monthly visits to the outpatient clinic thereafter. Twenty-four hour Holter monitoring was performed on the day following ablation and as needed thereafter the follow-up period. Symptoms of AF along with documentation of an AF lasting ≥30 s on a surface 12-lead ECG or Holter monitor after a 2-month blanking period from ablation were used to identify recurrence [11]. The follow-up was performed until 12 months after ablation. Patients were followed without any anti-arrhythmic drugs after ablation. If AF recurrence was detected, patients were included into the AF-recurrent group, and the resumption of anti-arrhythmic drugs was considered.

Statistical analysis

The values are presented as mean ± standard deviation, together with 95% confidence intervals. The significance of differences between the groups was analyzed using the unpaired Student's *t*-test for continuous variables and χ^2 test for categorical variables. The receiver operating characteristic curve analyses were performed to determine the optimal cut-off values for predicting AF recurrence after ablation. Cox regression analysis was performed to adjust for potential confounding factors. All variables with *P*-values < 0.20 in the univariate analysis were included in the multivariate analysis. The outcome of ablation was plotted using a Kaplan–Meier survival curve and was compared using the log-rank test. A *P* value < 0.05 was accepted as statistically significant.

Results

Baseline patient characteristics and outcome of ablation

Table 1 shows baseline patient characteristics. The mean age of patients was 64 ± 11 years. Approximately half of the patients had hypertension, whereas only a small number of patients had other comorbidities. Before ablation, anti-arrhythmic drugs, β-blockers, and calcium-channel blockers were administered in 53%, 47%, and 11% of patients, respectively. The left atrial dimension was within the normal range, and the left atrial appendage flow velocity was preserved. The left ventricular dilatation was not observed, and the left ventricular ejection fraction was preserved.

AF did not recur in 157 (78%) patients during 12 months of the follow-up period. Accordingly, the patients were divided into two groups: the AF-recurrent group ($N = 44$) and the AF-free group ($N = 157$). On average, the AF-recurrent group was younger than the AF-free group (60 ± 12 years old vs. 64 ± 11 years old, $P = 0.042$; Table 1) and had a higher proportion of patients who received anti-arrhythmic drugs before ablation. However, the remaining assessed characteristics were not different between the two groups.

Electrocardiographic findings

Table 2 shows electrocardiographic parameters measured before ablation. All electrocardiographic parameters, including maximum PWD, P-wave dispersion, and CV-PWD, were not different between the groups. After ablation, PWD was significantly shortened in all 12 electrocardiographic leads (Supplementary Table 1). Furthermore, after ablation, the maximum PWD was decreased (125 ± 17 ms to 118 ± 16 ms, $P < 0.001$; Fig. 2A) and CV-PWD was increased (0.069 ± 0.023 to 0.077 ± 0.028, $P < 0.001$; Fig. 2C). However, the P-wave dispersion did not change (25 ± 7 ms to 26 ± 8 ms, $P = 0.343$; Fig. 2B) after ablation. Table 3 shows the electrocardiographic parameters measured after ablation. Sinus rate, PQ interval, QRS interval, and QT interval were not different between the AF-recurrent and AF-free groups. Among the P-wave parameters, maximum PWD was not different between the groups; however, P-wave dispersion and CV-PWD were larger in the AF-recurrent group than in the AF-free group (P-wave dispersion: 28 ± 7 ms vs. 25 ± 8 ms, $P = 0.047$; CV-PWD: 0.090 ± 0.037 vs. 0.073 ± 0.024, $P < 0.001$).

Table 4 shows the accuracy of the P-wave parameters measured after ablation for the prediction of AF recurrence. CV-PWD achieved the highest diagnostic accuracy among the P-wave parameters. CV-PWD had an area under the curve (AUC) of 0.702; sensitivity, specificity, and positive and negative predictive values were 68%, 69%, and 38% and 88% for the cut-off value of 0.080, respectively. Table 5 shows the adjustment for potential confounding factors of AF recurrence. According to the results of a univariate Cox regression analysis, age, hypertension, and CV-PWD were included in a multivariate Cox regression analysis. Consequently, the predictive ability of CV-PWD for AF recurrence was independent of other clinical properties (Hazard ratio 3.180, 95% confidence interval 1.656 to 6.108, $P = 0.001$).

Table 1
Baseline patient characteristics.

	All patients ($n = 201$)	AF-recurrent group ($n = 44$)	AF-free group ($n = 157$)	*P* value
Age, years	64 ± 11	60 ± 12	64 ± 11	0.042
Male gender	147 (73)	33 (75)	114 (73)	0.901
Congestive heart failure	14 (7)	1 (2)	13 (8)	0.294
Hypertension	94 (47)	16 (36)	78 (50)	0.163
Diabetes mellitus	24 (12)	4 (9)	20 (13)	0.691
Past history of stroke	18 (9)	4 (9)	14 (9)	>0.999
Antiarrhythmic drugs	107 (53)	32 (73)	75 (48)	0.006
β-blockers	95 (47)	24 (55)	71 (45)	0.355
Calcium-channel blockers	23 (11)	7 (16)	16 (10)	0.432
Left atrial appendage flow velocity, cm/s	69 ± 25	68 ± 27	69 ± 25	0.772
Left atrial dimension, mm	39 ± 6	40 ± 6	39 ± 6	0.355
Left ventricular end-diastolic dimension, mm	48 ± 6	48 ± 6	48 ± 6	0.897
Left ventricular ejection fraction, %	64 ± 9	64 ± 9	64 ± 9	0.757
B-type natriuretic peptide, pg/ml	61 ± 92	62 ± 90	61 ± 93	0.941

Data are mean ± SD or number (%) of patients. AF, atrial fibrillation.

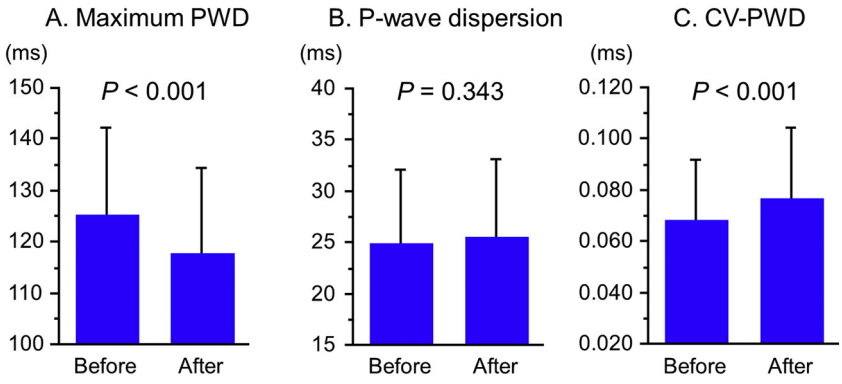

Fig. 2. Changes in P-wave parameters after ablation. Changes in maximum PWD (A), P-wave dispersion (B), and CV-PWD (C) are shown.

Table 2
Electrocardiographic parameters measured before ablation.

	All patients ($n = 201$)	AF-recurrent group ($n = 44$)	AF-free group ($n = 157$)	*P* value
Sinus rate, bpm	62 ± 12	62 ± 12	62 ± 12	0.895
PQ interval, ms	176 ± 28	173 ± 26	177 ± 28	0.434
QRS duration, ms	107 ± 17	107 ± 17	106 ± 17	0.988
QT interval, ms	417 ± 39	421 ± 43	416 ± 38	0.464
Maximum PWD, ms	125 ± 17	124 ± 18	126 ± 17	0.548
P-wave dispersion, ms	25 ± 7	24 ± 7	25 ± 7	0.321
CV-PWD	0.069 ± 0.023	0.069 ± 0.023	0.069 ± 0.023	0.990

Data are mean ± SD. AF, atrial fibrillation; CV-PWD, coefficient of variation of P-wave duration; PWD, P-wave duration.

Table 3
Electrocardiographic parameters measured after ablation.

	All patients ($n = 201$)	AF-recurrent group ($n = 44$)	AF-free group ($n = 157$)	*P* value
Sinus rate, bpm	76 ± 12	76 ± 13	76 ± 12	0.867
PQ interval, ms	165 ± 20	162 ± 19	166 ± 20	0.172
QRS duration, ms	104 ± 17	102 ± 16	104 ± 17	0.474
QT interval, ms	384 ± 34	384 ± 37	385 ± 34	0.885
Maximum PWD, ms	118 ± 16	114 ± 18	119 ± 16	0.117
P-wave dispersion, ms	26 ± 8	28 ± 7	25 ± 8	0.047
CV-PWD	0.077 ± 0.028	0.090 ± 0.037	0.073 ± 0.024	<0.001

Data are mean ± SD. AF, atrial fibrillation; CV-PWD, coefficient of variation of P-wave duration; PWD, P-wave duration.

Fig. 3 shows the difference in AF-free survival between groups stratified by cut-off values of P-wave parameters. The difference in AF-free survival rate between high maximum PWD patients (maximum PWD ≥ 117 ms) and low maximum PWD patients (maximum PWD < 117 ms) did not reach statistically significance (84% vs. 73%, $P = 0.067$; Fig. 3A); however, AF-free survival rate was significantly lower in high P-wave dispersion patients (P-wave dispersion ≥27 ms) than in low P-wave dispersion patients (P-wave dispersion <27 ms) (69% vs. 86%, $P = 0.005$; Fig. 3B). Furthermore, AF-free survival rate was significantly lower in high CV-PWD patients (CV-PWD ≥ 0.080) than in low CV-PWD patients (CV-PWD < 0.080) (65% vs 88%, $P < 0.001$; Fig. 3C).

Discussion

In this study, we assessed the impact of P-wave parameters, determined using a computerized automated measurement system, on AF recurrence after ablation in patients with paroxysmal AF. Consequently, we found that CV-PWD and P-wave dispersion assessed after ablation were associated with AF recurrence. In particular, CV-PWD had the highest predictive accuracy among P-wave parameters. Furthermore, the predictive ability of CV-PWD for AF recurrence was independent of other clinical parameters.

P-wave morphology represents atrial electrical activity, which depends on the size and shape of the atrial chambers and the velocity of electrical activation [12]. Moreover, atrial remodeling provides the substrates for AF by altering atrial electrical activity. Therefore, some previous studies have shown the relationship between P-wave morphology and AF development. For instance, atrial remodeling prolongs PWD by causing a conduction delay in the atria; thus, prolongation of PWD is associated with AF occurrence [13–15] and AF recurrence after ablation [16].

Furthermore, atrial remodeling causes conduction heterogeneity in the atria [3–5]; therefore, P-wave parameters representing atrial conduction heterogeneity indicate AF development. P-wave dispersion is one of the most important parameters representing atrial conduction heterogeneity. Previous studies have reported that P-wave dispersion was associated with new onset of AF [17,18], progression from paroxysmal to persistent AF [19], occurrence of AF after surgical procedures [20], and AF recurrence after ablation [9]. However, because the calculation of P-wave dispersion includes only the maximum and minimum PWD, it may not adequately represent atrial conduction heterogeneity. P-wave dispersion may be affected by the morphology of the atria, because the longest and shortest sides of the atria may be related to the maximum and minimum PWD, respectively. Additionally, P-wave dispersion is strongly affected by the measurement errors of PWD, because an error in just one lead could significantly affect P-wave dispersion.

Therefore, we devised CV-PWD to more accurately determine atrial conduction heterogeneity [10]. The calculation of CV-PWD includes PWDs measured in all 12 electrocardiographic leads; thus, CV-PWD seems less likely to be affected by the morphology of the atria. Furthermore, CV-PWD would not be greatly affected by the measurement

Table 4
Accuracy of electrocardiographic parameters for prediction of AF recurrence.

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Area under the curve	Cut-off value
Maximum PWD, ms	55	55	26	81	0.579	117
P-wave dispersion, ms	59	62	30	84	0.606	27
CV-PWD	68	69	38	88	0.702	0.080

Data are mean ± SD. AF, CV-PWD, coefficient of variation of P-wave duration; PWD, P-wave duration.

Table 5
Univariate and multivariate Cox regression analysis for recurrence of atrial fibrillation (AF) after ablation.

	Univariate		Multivariate	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age, years	0.978 (0.955 to 1.003)	0.080	0.977 (0.953 to 1.002)	0.068
Male gender	1.130 (0.554 to 2.305)	0.736		
Congestive heart failure	3.574 (0.491 to 26.005)	0.208		
Hypertension	1.534 (0.813 to 2.897)	0.187	1.228 (0.635 to 2.377)	0.541
Diabetes mellitus	1.328 (0.473 to 3.726)	0.590		
Past history of stroke	0.821 (0.293 to 2.303)	0.708		
Antiarrhythmic drugs	3.402 (0.463 to 24.995)	0.229		
β-Blockers	0.722 (0.390 to 1.338)	0.301		
Calcium-channel blockers	0.639 (0.283 to 1.441)	0.280		
Left atrial appendage flow velocity, cm/s	0.998 (0.986 to 1.011)	0.788		
Left atrial dimension, mm	1.019 (0.967 to 1.074)	0.476		
Left ventricular end-diastolic dimension, mm	0.994 (0.949 to 1.042)	0.808		
Left ventricular ejection fraction, %	0.992 (0.959 to 1.026)	0.630		
B-type natriuretic peptide, pg/ml	1.000 (0.997 to 1.003)	0.889		
CV-PWD ≥ 0.080	3.114 (1.631 to 5.945)	0.001	3.180 (1.656 to 6.108)	0.001

Data are mean ± SD or number (%) of patients. CI, confidence interval; CV-PWD, coefficient of variation of P-wave duration.

errors of PWD because any errors in one lead would be diluted out when calculating CV-PWD. Consequently, CV-PWD demonstrated a better predictive accuracy of AF recurrence than P-wave dispersion in this study. This finding is consistent with our previous study in which PWDs were manually measured [10].

Although we demonstrated the impact of P-wave dispersion and CV-PWD on AF recurrence after ablation, we did not observe a relationship between them before ablation. This study included patients with paroxysmal AF with normal left atrial dimension; hence, atrial remodeling was not found to be severe in our study subjects. Therefore, the impact of atrial remodeling on P-wave morphology may not have been large enough to be detected before ablation. The pulmonary veins largely contribute to P-wave morphology because they contain a mixture of myocardial and vascular tissues [21,22]. The finding that PWD was decreased after ablation suggests that pulmonary vein isolation has a significant impact on the P-wave morphology. Thus, residual AF substrates in the atria may have become apparent after ablation when the influence of pulmonary veins on P-wave morphology was eliminated. Furthermore, pulmonary vein isolation may have revealed potential atrial conduction heterogeneity by changing the sequence of atrial depolarization in the left atrium. This hypothesis is supported by our finding that CV-PWD increased after ablation.

Our study did not demonstrate a relationship between maximum PWD and AF recurrence. A previous study with a canine tachypacing AF model reported that atrial fibrosis did not decrease global atrial conduction velocity but increased atrial conduction heterogeneity [4]. Therefore, P-wave parameters representing atrial conduction heterogeneity may be more sensitive markers of atrial structural remodeling than maximum PWD, which is an index of atrial conduction delay.

The mechanisms of the variation of PWD among the various electrocardiographic leads remain unclear. Atrial conduction heterogeneity causes regional delays in atrial depolarization. As a result, activation time may differ throughout the atria. P waves recorded in different leads could be differentially affected by regional changes in atrial activation times, resulting in a variation of PWD among the electrocardiographic leads. If we consider the variation of PWD from the point of view of the atrial depolarization vector, another hypothesis can be made. P-wave amplitude decreases when the atrial depolarization vector is vertical to the axis of the recording lead. A decrease in P-wave amplitude causes false shortening of PWD. Atrial conduction heterogeneity may result in various changes in the atrial depolarization vector and may lead to the variation of PWD among the leads.

Clinical implications

Although alternative non-invasive tests, including Holter monitoring, signal-averaged electrocardiogram, and echocardiography, can be used to predict the risk of AF recurrence, the surface 12-lead ECG remains the simplest and most routinely used test for the evaluation of cardiac conditions. Therefore, CV-PWD, which is calculated on a surface 12-lead ECG, can be assessed at a low cost without any special equipment. Moreover, the computerized automated measurements eliminate

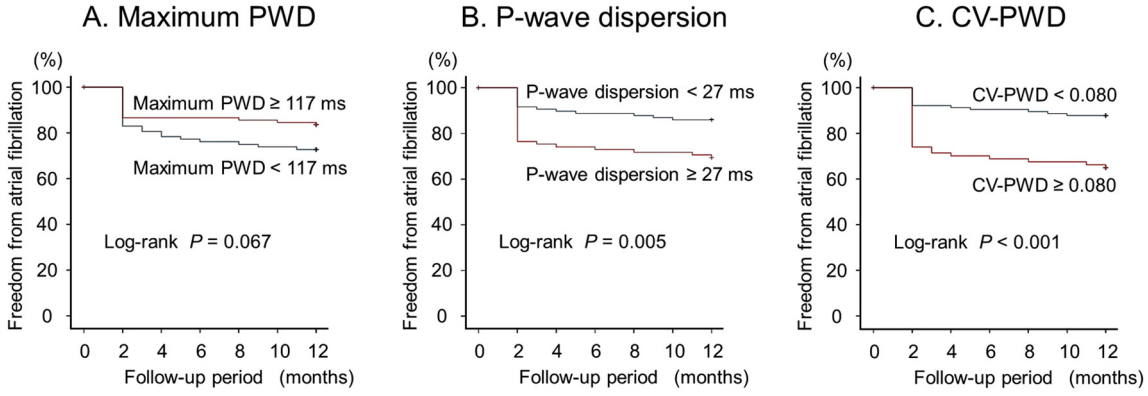

Fig. 3. Kaplan–Meier curves for atrial fibrillation-free survival according to high or low maximum PWD (A), P-wave dispersion (B), and CV-PWD (C). The cut-off values were determined by receiver operating characteristic curve analysis.

intra- and inter-observer variabilities and make it easy to assess CV-PWD in clinical practice.

Our study demonstrated that CV-PWD measured after ablation can be used to determine appropriate treatment strategies. If CV-PWD is high, an intensive follow-up should be performed to detect AF recurrence, and patients should resume anti-arrhythmic drugs. In patients with low CV-PWD, anti-coagulation medication may be discontinued because the negative predictive value of CV-PWD for AF recurrence was approximately 90%.

In our study, the impact of CV-PWD measured before ablation on AF recurrence was not observed; thus, CV-PWD cannot be used for patients who have received catheter ablation. However, CV-PWD measured before ablation may be associated with AF recurrence in patients with severe atrial remodeling, such as those with persistent AF. Further studies on patients with persistent AF may provide valuable information.

Study limitations

The present study was limited in several ways. First, the number of patients included in the present study was too small to draw definite conclusions. Second, because it is a retrospective study, the causal relationship is unclear. Third, although discontinuation of anti-arrhythmic drugs was included in the study protocol, it did not consider the discontinuation of calcium-channel blockers and β-blockers. However, the predictive ability of CV-PWD for AF recurrence was independent of the administration of calcium-channel blockers and β-blockers. Lastly, AF recurrence was diagnosed by a clinical interview and clinical examinations using a surface 12-lead ECG and a Holter monitor, a method that is well known for underestimating the prevalence of AF [23].

Conclusions

A computerized automated measurement of CV-PWD is useful for predicting AF recurrence after catheter ablation in patients with paroxysmal AF.

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