Discrimination of Paroxysmal and Persistent Atrial Fibrillation in Patients With New-Onset Atrial Fibrillation

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SUMMARY

Discrimination between paroxysmal and persistent atrial fibrillation (PAF and persistent AF) is important for determining the therapeutic strategy in patients with new-onset AF. We evaluated various clinical factors and P wave morphology to discriminate PAF and persistent AF patients in patients with new-onset AF.

The study population consisted of 79 patients with new-onset AF (70.3 ± 10.8 years, female:male 33:46) who were retrospectively selected from 8,632 AF patients in the Kitasato University Hospital ECG storing system. PAF ($n = 38$) and persistent AF ($n = 41$) patients were diagnosed by whether the initial PAF episode continued for 1 week. The P wave morphologies were analyzed using the most recent 12 lead-ECG recording of sinus rhythm. P wave dispersion was defined as the difference between the maximum and minimum durations of all leads. Along with these data, various clinical factors were evaluated and compared between PAF and persistent AF patients.

Multivariate analysis identified P wave dispersion (56.6 ± 14.8 versus 66.5 ± 12.8 msec, $P = 0.002$) and left atrial dimension (LAD: 40.2 ± 7.0 versus 47.7 ± 8.2 mm, $P < 0.001$) as independent factors for discrimination between PAF and persistent AF patients. Combining these two parameters achieved a specificity of 88.9%, a positive predictive value of 81.8%, a sensitivity of 95.3%, and a negative predictive value of 88.9%.

In patients with new-onset AF, P wave dispersion and LAD were independent factors for discrimination between PAF and persistent AF. (Int Heart J 2016; 57: 573-579)

Key words: P wave

In clinical practice, identification of the clinical stage of atrial fibrillation (AF) is an important issue to enable clinicians to determine a therapeutic strategy, especially in patients with new-onset AF, in whom it is important to determine the indication of antiarrhythmic agents or catheter ablation.¹⁻³ When considering catheter ablation for AF, it is important to identify the early stage of AF, ie, paroxysmal atrial fibrillation (PAF), because the efficacy of catheter ablation is higher in PAF patients, and the ablation procedure itself can be simplified.^{4,5} Recently, we have reported that P wave analysis in the 12-lead ECG of sinus rhythm is useful in determining the emergence of AF in clinical cases.⁶ We have shown that the P wave amplitude in lead II or V1 was higher, and P wave dispersion, ie, the dispersion of P wave duration, was larger in patients with new-onset AF compared with control patients without AF.⁶ Therefore, we hypothesized that the clinical stage of AF may also be identified by P wave analysis, as well as with the other clinical parameters. In the present study, we retrospectively identified patients with new-onset AF in the digital ECG profiling system of our hospital. Patients were classified into PAF and persistent AF by their clinical course in accord-

ance with the definitions in the AHA/ACC/ESC guidelines and JCS guidelines.^{7,8} P waves in the preceding sinus rhythm state were analyzed as the precursor state for new-onset AF. P wave data together with other clinical parameters were compared between patients with PAF and persistent AF to determine the clinical factors allowing discrimination between PAF and persistent AF.

METHODS

Study population: Between 2008 and 2012, a total of 106,921 12-lead ECG recordings were stored in the digital ECG profiling system of Kitasato University Hospital. Among these recordings, 8,632 patients exhibited AF. For selection of new-onset AF patients, patients with preceding clinical AF episodes were excluded. To enable us to analyze the P wave morphology during recent sinus rhythm, patients without a preceding sinus rhythm ECG recording within 12 months were also excluded. Patients prescribed class I or III antiarrhythmic agents were also excluded to eliminate the influence of antiarrhythmic

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agents on the P wave analysis. Finally, 79 patients were enrolled in this study. Patients were classified into PAF and persistent AF patients by the following 1-week observation in accordance with the definitions in the AHA/ACC/ESC and JCS guidelines.^{7,8)} In this study, persistent AF patients had documented AF on an ECG more than 1 week after the first documented AF (without sinus rhythm during this period) when patients visited or were hospitalized. Various clinical parameters, including P wave morphology, were evaluated in these patients and were compared between the two groups (Figure 1).

For all patients, clinical data, including blood chemistry and echocardiographic data, were evaluated retrospectively from routine examinations of each patient in an outpatient clinic. For the echocardiography (SONOS 7500; Philips, Andover, MA, USA), chamber dimensions were measured in the standard parasternal long-axis view, and the left ventricular ejection fraction was calculated using the area-length method.⁹⁾ All studies were conducted with the approval of the Ethics Committee of Kitasato University Hospital. Written informed consent was obtained from patients whenever possible, and was received from 32 of 79 patients by retrospective explanation or contact using a letter or fax.

Analysis of the P wave: For all patients, body-surface 12-lead ECG was recorded (FCP-7541; Fukuda Denshi Co, Ltd, Tokyo) using a standard gain of 0.1 mV/mm and a recording speed of 25 mm/s. For the P wave analysis, the most recent ECG recording of sinus rhythm preceding the new-onset AF episode within 12 months was used. Sinus rhythm was con-

firmed from the P wave axis of 0–90 degrees in the frontal plane and 0–90 degrees in the horizontal plane.¹⁰⁾ In each ECG trace, durations and amplitudes of the P waves were evaluated in all 12 leads. The onset and offset points of the P waves were determined as the intersection point of the upward or downward deflection of a P wave and the isoelectric line.^{11,12)} When the P waves exhibited biphasic forms, the latter negative phase was also included in the P wave duration (Figure 2). The P

Figure 1. Study population. Of 8,632 AF patients with 12-lead ECG recordings, 79 new-onset AF patients were selected by excluding patients with preceding AF episodes, without preceding sinus rhythm ECG recording within 12 months, or with prescription of class I or III antiarrhythmic agents. Utilizing the following 1 week observation, patients were classified into PAF and persistent AF groups. See text for details.

Figure 2. Analysis of P waves. Representative examples of sinus rhythm P wave analysis in a 12-lead ECG recording. The onset and offset points of the P wave were determined as the intersection point of upward or downward deflection of the P wave and the isoelectric line (A–C). When a P wave exhibited a biphasic form, the latter negative phase was also included in the measurement of P wave duration (D). The P wave amplitude was measured as the height of the peak of positive deflection or depth of the bottom of negative deflection from the isoelectric line of the onset point (A–C). In the biphasic P wave, the P wave amplitude was measured as the difference between the positive peak and the negative bottom of the recording (D). See text for details.

Table I. Clinical Characteristics of Patients and Univariate Analysis

	Total <i>n</i> = 79	PAF <i>n</i> = 38	Persistent AF <i>n</i> = 41	<i>P</i>
Age (years)	70 ± 11	68 ± 12	72 ± 10	0.124
Gender (M:F)	46:33	23:15	23:18	0.690
BMI (kg/m ²)	21.7 ± 10.8	21.8 ± 3.9	21.7 ± 3.7	0.970
Smoking <i>n</i> (%)	38 (50.7)	17 (22.7)	21 (28.0)	0.570
Underlying disease				
Congestive heart failure <i>n</i> (%)	25 (31.7)	6 (7.6)	19 (24.1)	0.004*
Ischemic heart disease <i>n</i> (%)	23 (29.2)	10 (12.7)	13 (16.5)	0.612
Dilated cardiomyopathy <i>n</i> (%)	1 (1.3)	0 (0.0)	1 (1.3)	0.342
Hypertrophic cardiomyopathy <i>n</i> (%)	3 (3.8)	2 (2.5)	1 (1.3)	0.514
Left ventricular hypertrophy <i>n</i> (%)	13 (16.5)	4 (5.1)	9 (11.4)	0.174
Valvular heart disease <i>n</i> (%)	6 (7.6)	0 (0.0)	6 (7.6)	0.014*
Hypertension <i>n</i> (%)	58 (73.4)	23 (29.1)	35 (44.3)	0.013*
Diabetes mellitus <i>n</i> (%)	25 (31.6)	8 (10.1)	17 (21.5)	0.051
Hyperlipidemia <i>n</i> (%)	38 (48.1)	12 (15.2)	26 (32.9)	0.005*
Vascular disease <i>n</i> (%)	7 (8.9)	1 (1.3)	6 (7.6)	0.061
ECG parameters				
Heart rate (sinus) (bpm)	69 ± 14	70 ± 16	67 ± 13	0.402
Heart rate (AF) (bpm)	98 ± 28	103 ± 30	93 ± 24	0.114
Maximum P wave duration (msec)	106.6 ± 15.5	103.4 ± 16.9	109.5 ± 13.6	0.082
P wave dispersion (msec)	61.7 ± 14.6	56.6 ± 14.8	66.5 ± 12.8	0.002*
P wave amplitude in II (mV)	0.165 ± 0.055	0.170 ± 0.009	0.160 ± 0.009	0.424
P wave amplitude in V ₁ (mV)	0.149 ± 0.084	0.149 ± 0.014	0.149 ± 0.013	1.000
UCG parameters				
Left atrial dimension (mm)	44 ± 9	40 ± 7	48 ± 8	<0.0001*
Left ventricular ejection fraction (%)	62 ± 10	61 ± 10	63 ± 9	0.440
Left ventricular diastolic dimension (mm)	50 ± 7	48 ± 6	52 ± 8	0.021
Blood chemistry				
BNP (pg/mL)	226.8 ± 374.6	205.2 ± 269.6	244.5 ± 445.1	0.670
Cr (mg/dL)	1.03 ± 0.76	1.01 ± 0.79	1.05 ± 0.12	0.804
eGFR (mL/minute)	64.3 ± 25.7	66.6 ± 27.4	62.3 ± 24.1	0.460
HbA1c (%)	5.4 ± 2.1	4.8 ± 2.5	6.0 ± 1.3	0.004*
LDL cholesterol (mg/dL)	106.9 ± 34.8	102.3 ± 35.2	110.3 ± 34.6	0.362
TG (mg/dL)	128.8 ± 74.1	142.2 ± 90.6	117.8 ± 56.1	0.173
Prescription				
ARB/ACEI <i>n</i> (%)	37 (46.9)	13 (16.5)	24 (30.4)	0.031*
Spironolactone <i>n</i> (%)	8 (10.2)	1 (1.3)	7 (8.9)	0.034*
β-blocker <i>n</i> (%)	31 (39.3)	10 (12.7)	21 (26.6)	0.024*
Ca-blocker <i>n</i> (%)	28 (35.4)	11 (13.9)	17 (11.5)	0.244
Statin <i>n</i> (%)	25 (31.6)	8 (10.1)	17 (21.5)	0.051

BMI indicates body mass index; BNP, brain natriuretic peptide; Cr, creatinine; eGFR, estimated glomerular filtration rate; LDL cholesterol, low-density lipoprotein cholesterol; TG, triacylglycerol; ARB, angiotensin receptor blocker; and ACEI, angiotensin converting enzyme inhibitor. *Statistical significance.

wave amplitude was measured as the height of the peak of positive deflection or the depth of the bottom of negative deflection from the isoelectric line of the onset point. In the biphasic P waves, the P wave amplitude was measured as the difference between the positive peak and the negative bottom of the recording (Figure 2). In the present study, positive deflections of P waves were also included into the analysis to salvage the electrophysiological properties of the right atria.¹³⁾ When there was difficulty in the determination of the onset or offset points of the P wave due to low P wave amplitude, data from the associated lead was excluded from the analysis. The digitally-stored ECG signals with time and amplitude resolutions of 1 msec and 0.001 mV, respectively, (FCP-7541; Fukuda Denshi Co, Ltd, Tokyo) were used for P wave evaluation. The analyses were performed by 2 investigators blinded to the other clinical parameters, and the means of their measurements were used. When the difference between the 2 investigators exceeded 12 msec in duration or 0.03 mV in amplitude, onset-

offset or peak-bottom points were discussed between the 2 investigators for the data adjustment. For the P wave analysis, durations and amplitudes of the P waves in leads II and V1 and the maximum P wave duration in the 12 leads were used as analysis parameters.¹⁴⁻¹⁶⁾ In addition, the dispersion of the P wave duration (P wave dispersion) was calculated by subtracting the minimum P wave duration from the maximum P wave duration among the 12 leads.^{11,12,14-17)}

Statistical analysis: All clinical data were compared between the PAF and persistent AF groups by univariate analysis to determine useful indices for discriminating between PAF and persistent AF patients. Multivariate analysis was performed using the parameters that showed a *P* value of < 0.1 in the univariate analysis by a stepwise method to identify the independent factors that predict persistent AF patients. This parameter selection was employed to eliminate various correlated parameters in our relatively small sized study population. For the independent predictive factors, receiver-operating characteristic

Table II. Multivariate Analysis of Clinical Parameters for Discrimination Between Persistent AF and PAF Patients

	Odds ratio	95% CI	P
Maximum P wave duration (msec)	0.94	0.87-1.00	0.0511
P wave dispersion (msec)	1.11	1.04-1.21	0.0014*
Left atrial dimension (mm)	1.15	1.06-1.27	0.0003*
HbA1c (%)	1.53	0.92-2.33	0.0644

*Statistical significance.

Figure 3. ROC curves for determination of PAF and persistent AF patients. ROC curves of P wave dispersion and LAD for determination of persistent AF patients in logistic regression analysis. The arrows indicate the optimal cut-off points for determination of PAF and persistent AF patients in each parameter. P wave dispersion achieved a sensitivity of 53.7% and specificity of 73.7% by setting the cut-off point at P wave dispersion > 65.0 msec ($P = 0.0014$, area under curve [AUC] 0.693, A). Left atrial dimension achieved a sensitivity of 80.5% and specificity of 58.8% by setting the cut-off point at left atrial dimension > 42.0 mm ($P = 0.0003$, AUC 0.742, B). See text for details.

(ROC) curves were obtained by logistic regression analysis. The optimal cutoff point was determined to achieve the highest sensitivity and specificity for each ROC curve for the determination of persistent AF patients. Finally, the c-statistics using significant parameters were calculated.

The JMP 10 (SAS Japan Inc., Tokyo) statistical software package was used for statistical analysis. Student's *t*-test or the Mann-Whitney *U* test was used to compare continuous variables, which are presented as the mean $\pm$ standard deviation. The χ^2 test was used to compare dichotomous variables, which are presented as percentages. Logistic regression analysis was performed to obtain ROC curves. A Cox hazard model was used for multivariate analysis. *P* values of < 0.05 were considered to indicate statistical significance.

RESULTS

Clinical characteristics of patients and univariate analysis:

Clinical profiles and characteristics of the study population are summarized in Table I. The incidence of underlying disease

was higher in persistent AF patients than in PAF patients, and significant differences in the presence of congestive heart failure, valvular heart disease, hypertension, and hyperlipidemia were observed between the groups. P wave dispersion ($P = 0.002$), left atrial dimension (LAD) ($P < 0.0001$), and left ventricular diastolic dimension ($P = 0.021$) were significantly larger in persistent AF patients compared with PAF patients. Hemoglobin A1c (HbA1c) levels were higher in persistent AF patients ($P = 0.004$). Prescription of various cardiovascular-active medicines was also more frequent in persistent AF patients than in PAF patients (Table I).

Multivariate analysis: For the multivariate analysis, parameters were selected by the stepwise method from those which exhibited $P < 0.1$ in the univariate analysis to avoid inappropriate repeated selection of parameters in similar categories. As a result, maximum P wave duration, P wave dispersion, LAD, and hemoglobin A1c were selected, and P wave dispersion and LAD were identified as independent factors for discrimination between PAF and persistent AF patients (Table II).

Discrimination between PAF and persistent AF: Figure 3 shows the ROC curves of P wave dispersion and LAD for de-

Table III. Discrimination of Patients by P wave Dispersion and LAD Diagnosis as Non- PAF Patients

	PWD > 65 msec	LAD > 42 mm	PWD > 65 msec and LAD > 42 mm	PWD > 65 msec or LAD > 42 mm
Sensitivity	0.537	0.805	0.419	0.953
Specificity	0.737	0.588	0.889	0.444
Positive predictive value	0.688	0.702	0.818	0.672

PWD indicates P wave dispersion.

termination of persistent AF patients in the logistic regression analysis. The most significant cut-off point was > 65.0 msec for P wave dispersion, with a sensitivity of 53.7% and a specificity of 73.7%, and > 42.0 mm for LAD, with a sensitivity of 80.5% and a specificity of 58.8%. Table III shows the results using P wave dispersion of > 65 msec and/or LAD of > 42 mm as the criteria for discrimination between PAF and persistent AF patients, which together achieved a specificity of 88.9% and a positive predictive value of 81.8%. In contrast, use of P wave dispersion of > 65 msec or LAD of > 42 mm achieved a sensitivity of 95.3% and a negative predictive value of 88.9%. The c-statistics of predicting persistent AF improved from 0.742, 0.693 to 0.799 by adding P wave dispersion to LAD.

DISCUSSION

The present study evaluated the differences in various clinical parameters between PAF and persistent AF patients, demonstrated with several interesting findings. First, several clinical parameters, including underlying diseases, P wave dispersion, LAD, HbA1c level, and the prescription of various cardiovascular-active medicines, showed significant differences between PAF and persistent AF patients in the univariate analysis. Second, P wave dispersion and LAD were identified as independent factors for discrimination between PAF and persistent AF patients in the multivariate analysis. Finally, when the optimal cut-off points of these two parameters were used as criteria for discrimination between PAF and persistent AF patients, the combination of the two achieved relatively high sensitivity (88.9%) and specificity (95.3%).

Parameters to discriminate between PAF and persistent AF: Several studies have reported the importance of P wave dispersion as a marker of the clinical phase of AF,¹⁸⁻²⁰ suggesting that P wave dispersion may be prolonged with progression of the AF phase, ie, the change from the PAF to persistent AF phase. Furthermore, Koide, *et al* concluded that P wave dispersion measurement may be useful in determining the progression of the clinical phase of AF.¹⁹ In the present study, multivariate analysis identified P wave dispersion as an independent factor for discrimination between PAF and persistent AF patients, consistent with previous reports. The mechanism of such significance of P wave dispersion is unclear. In the consideration of single and same P wave vector in the ECG recording, some investigators have doubted the clinical usefulness of this dispersion, but our present and preceding studies and other investigators have stated that the P wave dispersion is a useful index with which to evaluate atrial electrophysiology.^{6,11,12,14-16,19} Because P wave dispersion is the relative parameter calculated from the other measurements, correction or ad-

aptation of direct value by P wave duration or heart rate might be a possible method to obtain a parameter with absolute meaning, but because we could not find such a trial about correction in dispersion in the previous reports, we just used direct data of dispersion in this study. The mechanism underlying P wave dispersion change remains uncertain, but may partially be explained by the change in direction of the atrial activation vector. The atrial activation time is speculated to be prolonged along with the progression of AF, due to the atrial enlargement and tissue degeneration as a result of atrial structural remodeling in AF patients.^{14,21,22} Several studies have suggested that these changes may directly result in the prolongation of P wave duration,²³⁻²⁵ but may also influence the atrial activation vector. In particular, the terminal portion of the atrial activation vector may be generated by a smaller amount of atrial tissue, resulting in a smaller amplitude signal. This activation may be recorded in some leads, but is likely to not be detected in leads with a horizontal angle to the direction of vector.^{6,16,26} This phenomenon may result in the pseudo-disappearance of the terminal portion of the P wave in some leads, resulting in the enlargement of P wave dispersion in all 12 leads. In the present study, P wave duration also tended to be longer in persistent AF patients than in PAF patients, but the difference was not significant. In contrast, P wave dispersion exhibited a significant difference between the two groups, indicating that P wave dispersion was a more sensitive parameter in discriminating the clinical phase of AF in the present study population.

The present results also suggested LAD may be another parameter for discrimination between PAF and persistent AF patients, consistent with previous studies reporting an association between LAD and AF clinical history.^{18,27-29} However, the underlying cause of LA enlargement may be more complicated than the above explanation. Because we selected "new-onset AF" patients in the present study, LA enlargement may not only be due to AF, but may also be influenced by other underlying conditions. Although underlying diseases were not selected in the multivariate analysis using the stepwise method, univariate analysis showed higher prevalence of congestive heart failure, valvular heart disease, and hypertension in persistent AF patients, suggesting such underlying diseases may support atrial conditions more suitable for AF persistence, even before the clinical onset of AF.

Combined use of two parameters to discriminate between PAF and persistent AF: Koide, *et al* reported that the progression of PAF to persistent AF can be predicted by P wave dispersion, with a sensitivity of 71%, specificity of 77%, positive predictive value of 63%, and negative predictive value of 83%.¹⁹ Similarly, they reported that such AF progression can be detected by LA enlargement with a sensitivity of 64%, specificity of 76%, positive predictive value of 59%, and negative predic-

tive value of 79%.¹⁸⁾ In the present study, although we identified P wave dispersion and LAD as independent predictive factors for discrimination between PAF and persistent AF patients, the sensitivity and specificity of each parameter for PAF and/or persistent AF discrimination were limited (Table III). However, combination of both parameters achieved very high sensitivity and specificity, which may be useful for distinguishing PAF from persistent AF patients in clinical practice.

Clinical implications: The efficacy of rhythm control therapy is much higher in PAF patients than in persistent AF patients, regardless of a pharmacological or non-pharmacological, ie, catheter ablation, approach. Thus, a diagnosis of PAF strongly supports the choice of rhythm control therapy in clinical practice.^{1,30)} This discrimination also enables evaluation of catheter ablation efficacy as well as the necessity of additional procedures for standard pulmonary vein isolation, ie, linear ablation, continuous fractionated atrial electrogram ablation, and/or ganglionated plexi ablation.^{1,4,31,32)} Additionally, because the discrimination of PAF and persistent AF patients in the present study population was in “new-onset AF” patients, the present results are applicable for “first documented AF” patients. To the best of our knowledge, this is the first report which stated the parameters to discriminate between PAF and persistent AF patients in cases with “new-onset” AF. The clinical phase of AF is important in considering therapeutic strategy in AF patients; however, determination of the phase takes time, because it is usually accomplished after clinical observation.³³⁾ The present study has identified factors to discriminate the clinical phase of AF, including in “first documented AF” patients, which may be useful for choosing the appropriate therapeutic strategy in patients. Although several preceding manuscripts analyzing P wave and P wave dispersion in AF cases can be found, discrimination of PAF and persistent AF cases in ‘new-onset’ AF patients is a completely novel trial.

Limitations: The present study included several limitations. First, the size of the study population was relatively small, so that some parameters might be too enhanced in the analysis because of some patients with deviated data. Second, since the time resolution of screening AF in ECG recordings was too inaccurate, we might have failed to document “preceding” AF episodes even in our patient population of “new-onset AF”. This is the systematic limitation of this study. Third, because the measurement of P waves was based on morphological characterization, measurement errors may have been included to some degree. Finally, although the predictive factors for the clinical stage of AF in the present study showed good sensitivity and specificity, they were only evaluated in a limited study population, in which the predictive factors themselves had been determined by multivariate analysis. These issues should be resolved in a future prospective study with a larger patient population.

Conclusions: In patients with new-onset AF, P wave dispersion and LAD were independent factors for discrimination between PAF and persistent AF patients in multivariate analysis. Combination of both factors achieved high sensitivity, specificity, positive prediction value, and negative prediction value. These factors may be useful for the determination of clinical strategies in new-onset AF patients.

DISCLOSURE

This study received no financial support from commercial sources, and the authors state no conflicts of interest. There was no unapproved use of any compound or product.

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