Clues on electrocardiography to predict the presence of paroxysmal atrial fibrillation in patients with acute ischemic stroke: A propensity score-matched study

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ABSTRACT

Objectives: In this study, we aimed to detect surface electrocardiography (ECG) markers that could be predictive of paroxysmal atrial fibrillation (PAF) attacks in patients with ischemic stroke.

Patients and methods: Between November 2017 and April 2021, a total of 112 patients (65 males, 47 females; mean age: 70.5±6.8 years; range, 51 to 84 years) hospitalized for acute ischemic stroke with sinus rhythm on surface ECG who underwent Holter ECG monitoring for PAF were retrospectively analyzed. The patients were divided into two groups of 56 patients in each (Group 1: those with PAF on Holter ECG and Group 2: those without PAF). Both groups were matched according to demographic, clinical, and echocardiographic features using the propensity score matching method.

Results: Demographic, clinical, and echocardiographic features were similar between groups (p>0.05). The mean maximum P-wave duration (PWD) and P-wave dispersion (PWDis) were longer in Group 1 than Group 2 (108.4±9.9 ms vs. 102.5±10.2 ms; p=0.002, 49.4±13.6 vs. 36.8±11.7 ms; p<0.001). Similarly, the mean P-wave terminal force in lead V 1 (PTFV 1) was higher in Group 1 than Group 2 (4415±909 vs. 3826±568 µV·ms; p<0.001). Logistic regression analysis revealed high PWDis (odds ratio [OR]: 1.164; 95% confidence interval [CI]: 1.069-1.268; p<0.001) and PTFV 1 (OR: 1.156; 95% CI: 1.065-1.254; p=0.001) as independent predictors of PAF.

Conclusion: PWDis and PTFV 1 are independent predictors of PAF in patients with acute ischemic stroke. These simple and easily accessible predictors that can be detected via surface ECG may be used as a guide to identify patients who require longer rhythm monitoring to better detect occult PAF, thereby preventing recurrent strokes.

Keywords: Atrial fibrillation, ischemic stroke, P-wave dispersion, P-wave terminal force in lead V1.

Atrial fibrillation (AF) is one of the most frequent cardiac rhythm abnormalities. Although its prevalence in the general population is thought to be around 2 to 4%, it is expected that it would increase by 2.3 times as life expectancy increases and advanced investigation techniques lead to overdiagnosis.[1] Diabetes mellitus, advanced age, hypertension, chronic renal failure, coronary artery disease, heart failure, obesity and obstructive sleep apnea are all important predisposing factors for AF.[1,2] Also, AF can lead to serious complications such as heart failure, stroke and death.[3] While the risk of AF associated stroke is 1.5% in the sixth decade of life, this risk increases to 24% in the ninth decade.[4] Similar to clinically overt AF, paroxysmal atrial fibrillation (PAF) attacks also increase the risk of ischemic stroke. Current guidelines recommend monitoring with Holter electrocardiography (ECG) to detect PAF attacks in patients with ischemic stroke, even if the surface ECG is normal.[5] Currently, 24 to 48-h Holter ECG monitoring is used for this purpose. However, existing silent PAF attacks cannot be detected with these recordings in some cases. Identifying patients at high risk for the development of AF before resorting to Holter ECG monitoring may help to improve diagnostic accuracy. In such high-risk patients, monitoring may be extended, if AF is not detected on 24 to 48-h Holter ECG recordings, thereby preventing false-negative results.

Many previous studies have investigated the use of several different scoring systems to identify patients...
who are under high risk for development of AF.[6,7] However, many of these systems are complex and difficult to use in daily practice. In the present study, we aimed to determine surface ECG findings that could predict the presence of PAF in those with ischemic stroke.

**PATIENTS AND METHODS**

This single-centre, retrospective study was conducted at Izmir Bakırçay University, Department of Cardiology between November 2017 and April 2021. A total of 149 patients with an ischemic cerebrovascular event (CVE) that had sinus rhythm on baseline surface ECG and underwent 24 to 48-h Holter ECG for cardioembolic investigation were screened. The patients were matched with the propensity score matching method in terms of their baseline clinical, demographic, and echocardiographic characteristics, which may be risk factors for AF, at a ratio of 1:1, and 56 each with and without PAF on Holter ECG a total of 112 patients (65 males, 47 females; mean age: 70.5±6.8 years; range, 51 to 84 years) were included in the study. Those with PAF detected on Holter ECG were defined as Group 1 (n=56) and those without it were defined as Group 2 (n=56). Patients under 18 years of age, those with serious renal or hepatic insufficiency, rheumatic moderate to severe mitral valve stenosis, prosthetic heart valve, previous history of AF, those who did not have normal sinus rhythm on basal ECG and those with missing or insufficient data on ECG or Holter ECG records were excluded from the study. The study protocol was approved by the Bakırçay University Non-Interventional Clinical Research Ethics Committee (No: 2021-333). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients’ clinical, demographic, laboratory and ECG were obtained from the patient records. Baseline 12-lead surface ECG records were analyzed in detail. The 24 to 48-h Holter ECG recordings were evaluated by two cardiology specialists with the presence and length of PAF attacks noted.

**Electrocardiography**

During hospitalization with patients in the supine position, a 12-lead ECG was recorded from all subjects using 10 mV/cm standardization with 25 mm/sec paper speed and 0.05 to 100 Hz filter band settings. The ECGs were scanned and transferred to the computer system and measurements were made with an electronic caliper at 4× magnification on the high-resolution computer screen. P-wave dispersion (PWDis) was calculated as the difference between the maximum and minimum P wave duration (PWD) in all 12 ECG leads. P-wave terminal force in lead V1 (PTFV1) was defined as the duration multiplied by the amplitude of the negative part of the P wave (P’duration (a) × P’amplitude (b)), measured in µV ms in lead V1 (Figure 1).

Detection of an AF attack of at least 30 sec on Holter ECG was defined as PAF.

**Statistical analysis**

Statistical analysis was performed using the IBM SPSS for Windows version 25.0 software (IBM Corp., Armonk, NY, USA). A propensity score for the presence of PAF was estimated for each patient with logistic regression, using 26 clinically relevant baseline variables. Thereafter, using 1:1 matching without replacement, a matched cohort was constructed matching each patient without PAF to the closest patient with PAF in which propensity score differed by 0.1 or less. The ability to balance baseline features was evaluated by absolute standardized differences (the percentage difference between the means for the two groups divided by the reciprocal standard deviation). In standard differences, 10% were considered inconsequential. After matching, the overall balance p value was calculated as 0.99.

The normality distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test. Continuous variables were expressed in mean ± standard deviation (SD) and categorical variables were expressed in number and frequency. The groups were compared using the independent Student t-test or Mann-Whitney U test according to the normality distribution for continuous variables, and the chi-square test or Fisher exact test for categorical

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**Figure 1.** P-wave terminal force measurement in lead V1 (PTFV1) = (a) P’duration × (b) P’amplitude.

PTFV1: P wave terminal force in lead V1.
variables. The ECG findings were evaluated with logistic regression analysis to identify independent predictors of the presence of PAF on Holter ECG. Optimal cut-off values were determined by receiving operating characteristics (ROC) curve analysis to predict PAF. A \( p \) value of <0.05 was considered statistically significant.

### RESULTS

Previous to ischemic stroke, 61.6% of patients (n=69) had a diagnosis of hypertension, 41.1% (n=46) had hyperlipidemia, and 33.9% (n=38) had diabetes mellitus. A previous history of CVE was present in 17.9% (n=20) patients. Coronary artery disease was present in 24.1% (n=27) and chronic heart failure in

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (n=56)</th>
<th>Group 2 (n=56)</th>
<th>Standard differences</th>
<th>( p )</th>
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<td>19 33.9</td>
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<td>Hypercholesterolemia</td>
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<td>11 19.6</td>
<td>0.035</td>
<td>0.622</td>
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<td>0.825</td>
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<td>Carotid artery disease</td>
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<td>28 50</td>
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<td>CHA2DS2-VASc score</td>
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<td>LVEF (%)</td>
<td>57.7±5.7</td>
<td>58.1±4.2</td>
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<td>Left atrium diameter (mm)</td>
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<td>15 26.8</td>
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<td>Beta-blocker</td>
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<td>0.825</td>
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<td>21 37.5</td>
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<td>Levothyroxine</td>
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<tr>
<td>Methimazole</td>
<td>1 1.8</td>
<td>0 0</td>
<td>0.017</td>
<td>0.315</td>
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SD: Standard deviation; CVD: Cerebrovascular disease; COPD: Chronic obstructive pulmonary disease; LVEF: Left ventricular ejection fraction; LVDD: Left ventricular diastolic dysfunction; ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker.
6.3% (n=7) patients. Fifty-four (48.2%) patients had carotid artery disease and, of these patients, 34 had carotid artery stenosis <50% and 20 had stenosis ≥50%. The mean CHA2DS2-VASc score of patients was 4.9±1.3. The mean left ventricular ejection fraction was 57.9±5.1% and the mean left atrial (LA) diameter was 37.1±4.1 mm. When CVE occurred, 25% (n=28) patients were using acetylsalicylic acid, 17% (n=19) clopidogrel and 2.7% (n=3) were taking oral anticoagulant therapy. Patients’ demographic and clinical features are shown in Table 1 and their laboratory findings are shown in Table 2.

Both groups were similar with regard to the mean baseline heart rate (74.4±13.2 vs. 74.6±10.8 bpm, p=0.93). The mean maximum PWD and PWDis were longer in Group 1, compared to Group 2 (108.4±9.9 vs. 102.5±10.2 ms; p=0.002 and 49.4±13.6 vs. 36.8±11.7 ms; p<0.001, respectively). Similarly,
PTFV\textsubscript{1} was higher in Group 1, compared to Group 2 (4415±909 vs. 3826±568 µV·ms; p<0.001) (Table 3).

Logistic regression analysis demonstrated high PWDis (odds ratio [OR]: 1.164; 95% confidence interval [CI]: 1.069-1.268; p<0.001) and high PTFV\textsubscript{1} (OR: 1.156; 95% CI: 1.065-1.254; p=0.001) as being independent predictors for the presence of PAF (Table 4). As predictors for the presence of PAF, the ROC curve analysis revealed a sensitivity of 71% and specificity of 69% for PWDis >42 ms (area under the curve [AUC] 0.764, 95% CI: 0.675-0.852, p<0.001) and a sensitivity of 60% and specificity of 64% for PTFV\textsubscript{1} >4.050 µV·ms (AUC: 0.686, 95% CI: 0.574-0.798, p=0.002) (Figure 2).

**DISCUSSION**

In the present study, we found that PWDis and PTFV\textsubscript{1} parameters as measured on surface ECG were independent predictors for the presence of PAF in patients with ischemic stroke.

Some patients with AF describe palpitations, shortness of breath and fatigue while some may be completely asymptomatic and present with complications such as ischemic stroke or tachycardiomyopathy.[8] Non-valvular AF is responsible for about half of all cardioembolic events.[9] The incidence of occult or subclinical AF is not known. Therefore, patients with symptomatic AF that are observed in daily practice may be considered the tip of the iceberg. The development of new devices and applications has led to an increase in diagnosis rates of asymptomatic and subclinical AF. The rates of subclinical AF was reported to be 35% in a group of patients with implanted cardiac devices that were followed for 2.5 years.[10] In patients with cryptogenic stroke, 12.5% were found to have PAF attacks during one-year rhythm monitorization.[11] It is important to identify patients who do not have arrhythmia on surface ECG, but who are at high risk for the development of AF and to perform long-term rhythm monitoring in these patients to prevent ischemic stroke.

Many scoring methods have been utilized to predict the development of AF in those with normal surface ECG.[6,7] The CHADS2 and the CHA2DS2-VASc risk scores have been reported for prediction of new occurrence of AF, ischemic stroke and long-term outcomes after AF ablation.[12] Christophersen et
al.\cite{12} reported that CHARGE-AF scoring was better at predicting AF, compared to CHA2DS2-VASc. On the other hand, some studies have used the HATCH score for prediction of AF recurrence and persistence.\cite{13} The main feature of these scoring methods is that they predict the development of AF according to the clinical characteristics of the patients. However, AF is an ECG disorder and using ECG findings for its prediction may be a more plausible way. Electrocardiographic evaluation is also a simpler, cheaper, and easily accessible method than the aforementioned scoring systems. Furthermore, it has been reported that P-wave indices are as effective as clinical scoring methods for the prediction of AF and ischemic stroke.\cite{14} Several ECG indices thought to represent atrial remodeling have been independently associated with stroke and AF.\cite{15} These measures include the (i) PWD; (ii) PWDis; (iii) PTFV1 in the precordial lead V1; (iv) P-wave axis; and (v) interatrial blocks (IABs).\cite{16} Previous studies have identified several P-wave indices that are markers of LA dysfunction and are associated with ischemic stroke with or without AF.\cite{17} Previous studies have reported that maximum PWD may be used for the prediction of AF.\cite{18} However, we did not detect PWD to be a predictor for the presence of AF in our study.

P wave dispersion is considered to reflect impaired and heterogeneous interatrial conduction, which is a specific and sensitive marker of AF in a wide variety of conditions.\cite{19} Dilaveris et al.\cite{18} found that PWDis was significantly higher in patients with paroxysmal AF compared to the control group, and a PWDis value of 40 ms distinguished paroxysmal AF patients from the control group with a sensitivity of 83% and a specificity of 85%. Aytemir et al.\cite{20} reported PWDis >36 ms to be an independent predictor for the development of AF with a sensitivity of 77% and specificity of 82%. The PWDis has been used for the prediction of AF in several clinical situations such as hyperthyroidism, chronic obstructive pulmonary disease, acute ischemic stroke and hypertrophic cardiomyopathy.\cite{19} Doğan et al.\cite{21} reported PWDis as an independent predictor for the development of AF in patients with acute ischemic stroke. Similarly, we also found PWDis to be a predictor of PAF in patients with ischemic stroke, with a sensitivity of 71% and specificity of 69%.

The PTFV1 was first used by Morris et al.\cite{22} in 1964 as a representative of LA overload in several valvular heart diseases. Later, PTFV1 was found to be an indicator of various pathologies such as increased LA pressure, LA hypertrophy, LA enlargement, and abnormal interatrial conduction.\cite{17} Since AF development is also associated with these structural changes and electrical remodeling, PTFV1 may be a good predictor of AF development. PTFV1 >4000 µV·ms is accepted to be abnormal. An abnormal PTFV1 level has been shown to negatively affect prognosis in heart failure and myocardial infarction.\cite{23} It was reported that a 1-SD increase of PTFV1 increased the risk of AF occurrence by 27%.\cite{17} Additionally, PTFV1 was found to be a better predictor in hemodialysis and stroke patients compared to the normal population.\cite{17} The PTFV1 is indicative of LA volume overload and it has, therefore, been frequently used for AF prediction in patients undergoing hemodialysis.\cite{17} Goda et al.\cite{24} found PTFV1 to be a strong predictor of AF in patients with acute ischemic stroke. In addition, PTFV1 was reported to be a good predictor of stroke, regardless of AF in a meta-analysis by He et al.\cite{25} However, Sajeev et al.\cite{26} suggested that PTFV1 was a weak predictor of ischemic stroke. Similarly, we found that PTFV1 had a lower sensitivity and specificity in the detection of AF compared to PWDis.

There are some limitations in the current study. First, our sample size was relatively small, which may have weakened the strength of our results. Second, this study is retrospective in nature. Third, Holter ECG monitoring was performed for 24 to 48 h in all patients. If a longer follow-up could have been made, PAF attacks could have been detected in more patients.

In conclusion, PWDis and PTFV1 in lead V1 are independent predictors for the presence of PAF in patients with ischemic stroke. These simple and easily accessible predictors, which can be detected by surface ECG, may help in identifying patients that require longer rhythm monitoring to detect occult PAFs, thereby preventing recurrent strokes.

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