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Relationship between cryptogenic ischemic stroke and P wave peak time

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ABSTRACT

Objectives: This study aimed to examine whether P wave peak time (PWPT), a predictor of atrial fibrillation (AF), is significantly higher at the time of diagnosis in cryptogenic ischemic stroke patients.

Patients and methods: The retrospective was conducted with 118 individuals (72 males, 46 females; mean age: 66.4±13.8 years) with cryptogenic ischemic stroke in the patient group and 118 individuals (77 males, 41 females; mean age: 63.2±16.1 years) without cerebrovascular disease in the control group between January 2021 and December 2023. The groups were compared regarding PWPT.

Results: As a result of multivariate regression analysis, PWPT-D2 and PWPT-V1 were found to be independent predictors of cryptogenic ischemic stroke. In the ROC analysis, when PWPT-D2 was >51.5 msec, the sensitivity for the diagnosis of cryptogenic ischemic stroke was found to be 80%, and the specificity was 76%. When PWPT-V1 was >46 msec, the sensitivity for the diagnosis of cryptogenic ischemic stroke was found to be 75%, and the specificity was 73%.

Conclusion: P wave peak time is an important predictor of cryptogenic ischemic stroke. The reason for the high PWPT level in these patients may be undetected AF. Therefore, longer-term rhythm Holter may be recommended in these patients.

Keywords: Atrial fibrillation, electrocardiography, cryptogenic ischemic stroke, P wave peak time.

Atrial fibrillation (AF) is an important cause of cryptogenic stroke, and if AF is detected in these patients, anticoagulation is required to prevent recurrent strokes.[1] Studies have shown that the use of direct oral anticoagulant therapy in cryptogenic stroke patients is not superior to standard antiplatelet therapy.[2] This shows us the importance of detecting AF in cryptogenic stroke patients. However, the costs and availability of diagnostic devices in daily clinical routine make long-term heart rhythm monitoring challenging.[3] There is a need for simple and applicable diagnostic methods that can predict AF in patients with cryptogenic ischemic stroke where we cannot detect AF in its etiology for these reasons. Related studies have identified features of electrocardiography (ECG), echocardiography, and neuroimaging that are important for the diagnosis of AF in cryptogenic ischemic stroke patients.[4] Additionally, some laboratory biomarkers have been associated with AF in cryptogenic ischemic stroke patients.[5]

P wave parameters and indices derived from these parameters are used for measurements of atrial electrical activity in ECG. Additionally, these parameters and indexes are also used to detect the possibility of AF. Some studies have found that there is a direct correlation between abnormalities in the P wave and P wave-derived parameters and the risk of cerebrovascular events.[6] Parameters such as P wave duration and P wave peak time (PWPT) derived from

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the P wave have been found to be associated with AF and cerebrovascular events.[7]

This study aimed to examine whether PWPT, a predictor of AF, is significantly higher at the time of diagnosis in cryptogenic ischemic stroke patients. If the PWPT duration is significantly higher in cryptogenic ischemic stroke disease, longer follow-up with rhythm Holter may be recommended to detect AF in these patients since PWPT is an important predictive parameter for AF.[7] If AF is detected as a result of prolonged rhythm Holter duration in cryptogenic ischemic stroke patients, anticoagulant therapy could be considered in the treatment of these patients. In this way, mortality and morbidity could decrease in cryptogenic ischemic stroke patients.

PATIENTS AND METHODS

This retrospective study was conducted with 118 patients as patient group (72 males, 46 females; mean age: 66.4±13.8 years) with cryptogenic ischemic stroke at the Uşak University Training and Research Hospital between January 2021 and December 2023. In the control group, 118 patients (77 males, 41 females; mean age: 63.2±16.1 years) with similar baseline characteristics and without cerebrovascular disease were included. The patients were diagnosed with cryptogenic ischemic stroke by neurologists using radiological imaging. Patients with cryptogenic ischemic stroke were monitored with rhythm Holter for 72 h from the moment of diagnosis. Patients with previous cerebrovascular disease, patients with a history of AF, patients with pacemakers, patients with active infection, patients whose ECG was AF when diagnosed with cryptogenic ischemic stroke, patients with AF detected as a result of 72-h rhythm Holter after the diagnosis of ischemic stroke, patients with moderate and severe heart valve disease, patients with chronic renal failure, patients with congenital heart disease, patients with heart failure, patients with carotid artery disease, patients with hematological diseases, patients with rheumatological disease, and patients who did not have an ECG at the time of diagnosis were excluded from the study.

Electrocardiography at the time of diagnosis was transferred to digital media. P wave peak times were calculated and defined as the time from the beginning to the peak of the P wave, calculated from leads D2 and V1 (Figure 1). Electrocardiography parameters, echocardiography parameters, and blood parameters at the time of diagnosis were compared between the groups.

Statistical analysis

Data were analyzed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Histograms, the Shapiro-Wilk test, and q-q plots were used to understand whether the data were normally distributed. The Mann-Whitney U and T tests were applied to compare variables between the groups. The chi-square test was used for categorical variables. Logistic regression analysis was used to identify risk

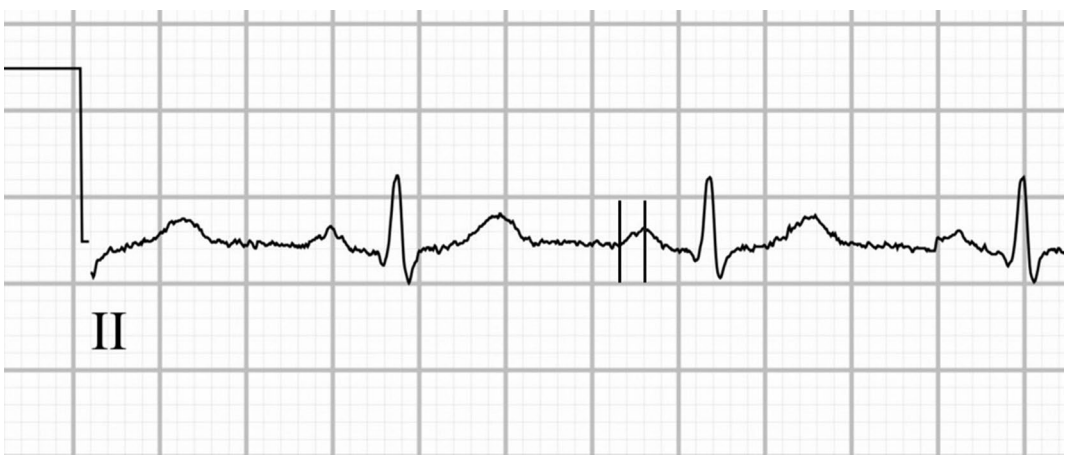

Figure 1. Calculation of PWPT-D2.
PWPT: P wave peak time.

factors affecting cryptogenic ischemic stroke. Variables found to be statistically significant as a result of logistic regression analysis were evaluated in multivariate logistic regression analysis. Receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic performance power of PWPT in lead D2 (PWPT-D2) and PWPT in lead V1 (PWPT-V1) in cryptogenic ischemic stroke disease. The area under the curve, cutoff value, sensitivity, and specificity were calculated for both parameters. The statistical significance level was accepted as $p<0.05$.

RESULTS

No cause of stroke was found in any of the 118 patients with cryptogenic ischemic stroke included in the study. As a result of comparing the variables in the patient and control groups, PWPT-D2 duration (58.9±9.8 and 48.4±7.6, respectively; $p<0.001$) and PWPT-V1 duration (56.9±8 and 47.5±8.7, respectively; $p<0.001$) were longer in patients with cryptogenic ischemic stroke. There was no significant difference between the two

Table 1
Comparison of variables between the groups

	Patient group (n=118)			Control group (n=118)			
Variables	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			66.4±13.8			63.2±16.1	0.14
Sex							
Female	46	38.9		41	34.7		0.47
Diabetes mellitus	50	42.3		45	38.1		0.08
Hypertension	69	58.4		63	53.5		0.07
Hyperlipidemia	48	40.6		45	38.1		0.34
CAD	31	26.2		24	20.3		0.06
Body mass index (kg/m^2)			26.3±3.7			25.9±3.6	0.53
PWPT-D2 (msec)			58.9±9.8			48.4±7.6	**<0.001**
PWPT-V1 (msec)			56.9±8			47.5±8.7	**<0.001**
Heart rate (per min)			81±9.7			79±8.2	0.41
Ejection fraction (%)			57.9±8.1			58.9±7.4	0.36
Left atrium diameter (mm)			38.2±5.8			37±5.9	0.15
White blood cell (10^3/uL)			8.8±3			8.3±2.9	0.28
Neutrophil (10^3/uL)			67.5±10.5			66.1±11.1	0.36
Lymphocyte (10^3/uL)			23.1±9.2			22.1±7.9	0.41
Hemoglobin (g/dL)			12.9±1.9			13.2±1.4	0.18
Platelet (10^3/uL)			252.5±89.8			257.2±82.8	0.27
Blood urea nitrogen (mg/dL)			37.7±14.8			36.1±16	0.45
Creatinine (mg/dL)			0.95±0.45			0.86±0.19	0.08
Sodium (mEq/L)			138.7±2.7			139.2±2.6	0.13
Potassium (mEq/L)			4.2±0.46			4.1±0.41	0.15
Glomerular filtration rate (mL/min)			81.3±25.7			83.7±24.7	0.50
Total cholesterol (mg/dL)			190.3±57.9			177.6±73.4	0.18
Triglyceride (mg/dL)			184.4±120.8			174.8±123.8	0.58
High density lipoprotein (mg/dL)			44.1±14.5			45.2±14.4	0.61
Low density lipoprotein (mg/dL)			105.1±37.9			102.9±38.8	0.69

SD: Standard deviation; CAD: Coronary artery disease; PWPT: P wave peak time.

Table 2
Univariate and multivariate logistic regression analysis

	Univariate			Multivariate		
Variables	OR	95% CI	*p*	OR	95% CI	*p*
PWPT-D2	1.156	1.103-1.212	**<0.001**	1.131	1.073-1.192	**<0.001**
PWPT-V1	1.132	1.089-1.177	**<0.001**	1.101	1.046-1.159	**<0.001**
Hypertension	1.462	0.947-2.112	0.10			
Diabetes mellitus	1.065	0.933-1.179	0.09			
Coronary artery disease.	1.013	0.912-1.213	0.07			
Hyperlipidemia	1.009	0.978-1.013	0.40			

OR: Odds ratio; CI; confidence interval; PWPT: P wave peak time.

groups in any parameter except for PWPT-D2 and PWPT-V1 (Table 1).

Regression analysis was performed to find parameters predictive of cryptogenic ischemic stroke. Coronary artery disease, hypertension, diabetes mellitus, hyperlipidemia, PWPT-D2, and PWPT-V1 were included in the univariate regression analysis. As a result of the multivariate regression analysis, PWPT-D2 and PWPT-V1 were found to be independent predictors of cryptogenic ischemic stroke (Table 2).

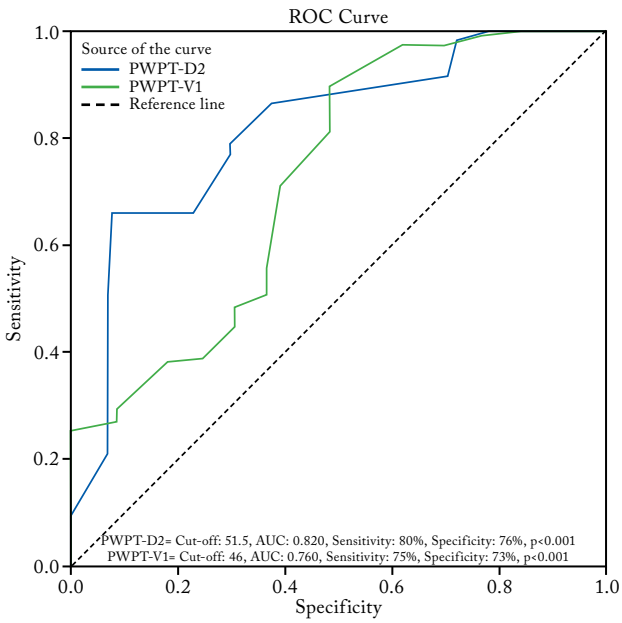

Figure 2. Receiver operating characteristic curve analysis for PWPT-D2 and PWPT-V1.
PWPT: P wave peak time.

In the ROC analysis, when PWPT-D2 was >51.5 msec, the sensitivity for the diagnosis of cryptogenic ischemic stroke was found to be 80%, and the specificity was 76%. When PWPT-V1 was >46 msec, the sensitivity for the diagnosis of cryptogenic ischemic stroke was found to be 75%, and the specificity was 73% (Figure 2).

DISCUSSION

This study helps elucidate the etiology of cryptogenic ischemic stroke. As a result of our study, we found that PWPT, which is a strong predictor of AF, was significantly higher in cryptogenic ischemic stroke patients at the time of diagnosis. This suggests that the cause of cryptogenic ischemic stroke disease is undetected AF.

Atrial fibrillation significantly increases the risk of ischemic stroke in patients.[8] Atrial fibrillation is known at the time of diagnosis in approximately 15 to 18% of patients with ischemic stroke or transient ischemic attack.[9] Therefore, the cause of stroke in the majority of these patients is AF.[9] In another study, it was found that 30% of patients who were diagnosed with AF before their stroke diagnosis also had AF when they were admitted to the hospital.[10] In the same study, it was found that 4 to 13% of patients whose AF diagnosis was unknown at the time of stroke had AF attacks during their follow-up.[10] In another study conducted independently of these, it was found that the first AF attack was detected in the ECGs taken at the time of diagnosis in 1.7 to 16% of patients with acute ischemic stroke or transient ischemic attack.[11] In the same study, the first AF attack was

detected in approximately 0.2 to 13% of all patients as a result of rhythm monitoring with an extra 24-h ECG.[11] In 72-h ECG rhythm monitoring, the first AF attack was detected in approximately 2.3 to 11% of ischemic stroke patients.[11] After rhythm monitoring with ECG for one week after stroke diagnosis, AF was diagnosed in 1.7 to 14% of all patients.[11] In a randomized controlled study conducted with stroke patients, the first AF attack was detected in 18 of 200 patients with 10-day rhythm Holter monitoring.[12] In the 10-day rhythm Holter follow-up performed after a three-month interval, the first AF attack was detected in 10 patients.[12] In the 10-day rhythm Holter follow-up performed after a six-month interval, AF was not found in any of the remaining stroke patients.[12] In a study conducted with patients diagnosed with cryptogenic ischemic stroke, the first AF attack was detected in 46 of 286 patients after rhythm monitoring for 30 days.[13] All this suggests that a new method is needed to find AF in patients with cryptogenic ischemic stroke. In our study, the prolonged detection of PWPT, which is a predictor of AF, in cryptogenic ischemic stroke patients should suggest AF. Patients with long PWPT should be evaluated for anticoagulant use. In addition, long-term and frequently intermittent rhythm Holter should be recommended to these patients. Already, the USA guideline recommends rhythm monitoring with ECG for 30 days to detect AF in patients diagnosed with cryptogenic ischemic stroke (Class 2A, Level C).[14] The European Society of Cardiology recommends rhythm monitoring with ECG to detect AF for at least 72 h from the moment of diagnosis in patients who have had a stroke or transient ischemic attack but do not have known AF (Class 1, Level B).[15] In our study, we fitted patients with a rhythm Holter to detect AF for 72 h from the stroke diagnosis. However, we did not find AF in any patient. In the European Stroke Organization guideline, it is recommended that rhythm monitoring be performed for a long time in stroke patients with the possibility of AF, but there is no information about the duration in acute strokes.[16]

Cryptogenic ischemic stroke accounts for one-quarter of ischemic strokes.[17] Cryptogenic ischemic stroke is more likely to be a recurrent stroke than other strokes. The probability of recurrence of ischemic stroke in these patients is between 3 and 6%.[18] Studies suggest new clinical scores in cryptogenic stroke patients with no etiology detected.[19] Although previous studies on this subject suggested long-term heart rhythm monitoring with implantable devices in cryptogenic stroke patients, this cannot be fully implemented.[20] Since the required effort and cost are quite high, the probability of being diagnosed with AF in this patient group in one year is approximately 10%.[20]

This supports the need to determine the etiology in patients with cryptogenic ischemic stroke. Although various risk factors for AF have been identified in previous studies, the use of a single predictor may not be sufficient to detect AF in patients according to large population-based studies.[21] For this reason, risk scores based on imaging, clinical evaluation, and echocardiographic features have been developed to detect AF in patients.[21] Although these scores provide important results for AF, such scores have not been developed in cryptogenic ischemic stroke patients.[21]

In a study, PWPT-D2 was found to be a significant predictor of paroxysmal AF in acute ischemic stroke patients.[22] The P wave shows us the conduction time between the sinoatrial node and the atrioventricular node.[22] There is restructuring in the atria in paroxysmal AF patients.[22] In addition, abnormal activities in the atria may cause changes in the structure of the atrium and affect the electrophysiological mechanism.[23] These changes can make significant changes on the P wave.[23] P wave parameters were found to predict poor clinical outcomes, such as AF, cerebrovascular accident, death, and heart failure.[24] P wave peak time is an important ECG parameter that is the subject of many articles.[22] In a study conducted on patients with coronary artery disease, a significant correlation was found between left atrial dysfunction and PWPT.[25] Additionally, in another study, it was found that the disease severity increased as the PWPT-D2 duration increased in coronary artery patients admitted with the diagnosis of non-ST-elevation myocardial infarction.[26] In addition to these published studies, another study conducted with hypertensive patients observed that left ventricular end-diastolic pressure increased as PWPT-D2 duration increased.[27] In a study investigating the relationship between silent ischemic stroke and PWPT, it was found that longer PWPT in leads D2 and V1 was associated with silent ischemic stroke, while PWPT-D2 was independently

associated with silent ischemic stroke.[23] In our study, PWPT-D2 and PWPT-V1 were found to be higher in the cryptogenic ischemic stroke patient group. Additionally, these two parameters were found to be independent predictors in the diagnosis of cryptogenic ischemic stroke.

Cardioembolic conditions constitute 25% of total ischemic strokes.[28] Cardioembolic strokes are associated with worse prognosis than noncardioembolic strokes.[29] Since the cause of the stroke in cryptogenic ischemic stroke patients is not identified, it is unclear whether there is a cardioembolic cause. However, as a result of our study, we detected PWPT prolongation in these patients and revealed the possibility of undetected AF in the etiology of cryptogenic ischemic stroke. In ischemic stroke patients, as the cardiovascular risk status increases and the ECG follow-up period increases, the probability of detecting AF also increases.[30] In our study, the rates of hypertension, coronary artery disease, hyperlipidemia, and diabetes mellitus were higher in the group with cryptogenic ischemic stroke, but there was no statistical difference compared to the other group. This situation may have caused the PWPT period to extend slightly. Prospective randomized controlled studies are needed to better understand this issue.

The main limitation of this study is the retrospective design. Multicenter studies with a large number of participants are needed to better understand whether PWPT detects AF in etiology in patients with cryptogenic ischemic stroke. To determine whether PWPT truly detects undetectable AF in cryptogenic ischemic stroke patients, it needs to be compared with a group of patients with ischemic strokes of different etiology other than AF, in addition to the existing control group. This situation creates a different limitation that is important for our study. Additionally, there was not enough follow-up time to detect AF in the patients. The inability to wear a rhythm Holter for longer than 72 h is also among the major limitations.

In conclusion, the high PWPT in patients with cryptogenic ischemic stroke of unknown etiology suggests that these patients have undetected AF in their etiology. Therefore, anticoagulant treatment may be considered in these patients to prevent recurrent strokes. Additionally, long-term rhythm Holter may be considered to detect AF in these patients.

Ethics Committee Approval: The study protocol was approved by the Uşak University Training and Research Hospital Ethics Committee (date: 06.01.2021, no: E-38824465-020-2221). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed equally to the article.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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