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Association Between Left Atrial Abnormalities and Cryptogenic Stroke Severity

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Abstract

Introduction: A growing body of evidence suggests a significant role for atrial abnormalities in the occurrence and severity of cryptogenic strokes; however, this role remains to be understood. This study examined the association of left atrial (LA) abnormalities with the severity of cryptogenic strokes.

Methods: A single-center, cross-sectional study was conducted among patients with cryptogenic stroke. We measured P-wave terminal force in Lead I (PTFV1) from standard 12-lead EKGs, with values > 5000 μV·ms considered abnormal and an indicator of atrial abnormalities. Patients were categorized into three groups based on their stroke severity assessed by the NIHSS score (mild, moderate, severe). EKG findings, particularly abnormal PTFV1 prevalence, were compared across these severity groups.

Results: The study included 130 patients (mean age 69 ± 14 years; 52.3% male). A total of 50 patients (38.5%) exhibited abnormal PTFV1 values. The prevalence of abnormal PTFV1 was significantly higher in patients with more severe strokes: 18.9% in the mild stroke group, 29.3% in the moderate stroke group, and 74.3% in the severe stroke group ($P < 0.001$). Univariate logistic regression identified age and abnormal PTFV1 as significant predictors of stroke severity.

Conclusion: The findings of this study reveal that PTFV1 abnormalities strongly correlate with the severity of cryptogenic strokes, highlighting the role of cardiac—particularly atrial—sources in their occurrence.

Keywords: Prevalence, Ischemic stroke, Electrocardiography, Stroke

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Introduction

The role of atrial abnormalities in cryptogenic stroke and prognosis has received increased attention in recent years, given the increasing long-term disabilities and mortality caused by cryptogenic strokes (1).

Cryptogenic stroke is a type of stroke with no possible explanation, even with diagnostic investigations for cardiovascular, hematological, and serological causes (2,3). It is a perplexing condition that affects about 30% to 40% of ischemic strokes (2).

Previous studies have identified patent foramen ovale (PFO) as a potential contributing cardiac abnormality in young adults with cryptogenic stroke (4). These findings highlight the importance of evaluating cardiac abnormalities in cryptogenic stroke and support further assessment of other atrial markers.

However, there are several variants associated with an increased risk of cryptogenic stroke, including hypertension, diabetes mellitus, hyperlipidemia, and smoking(2). Recent population-based evidence has also identified older age, male sex, and lower HDL levels as independent predictors of increased carotid intima-media thickness, emphasizing the importance of comprehensive vascular risk assessment (5). In addition, numerous studies have considered increased atrial size as a potential risk factor for ischemic and hemorrhagic stroke (6,7).

Some studies have suggested that there may be a correlation between cardiac structural abnormalities and stroke severity. (8). Kato et al. demonstrated that left atrial (LA) abnormality is associated with a higher risk for severe ischemic strokes (9).

Based on the National Institutes of Health Stroke Scale (NIHSS) classification, a widely accepted and validated tool for assessing stroke severity, stroke severity ranges from 0 to 42 (categorized as severe, moderate, or mild) (10,11).

One of the most potent and accessible metrics used to reveal LA abnormalities and atrial fibrosis is the P-wave terminal force (PWTF) in lead V1 (PTFV1) (12). PTFV1 reflects the

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degree of left atrial enlargement and remodeling, which can be caused by various conditions such as hypertension, valvular disease, or atrial fibrillation. Abnormal PTFV1 is associated with an increased risk of ischemic stroke, heart failure, and sudden cardiac death (13).

PTFV1 can be easily calculated using a standard 12-lead ECG by measuring the amplitude and duration of the negative P-wave in lead V1. A PTFV1 of more than −40 mm·ms theoretically reflects left atrial geometric changes in diastolic dysfunction due to delayed electrical propagation in the atrial tissue (14).

Although a number of articles have suggested the connection between LA abnormalities and stroke severity (15), the experimental data are highly contested, and there is no universal consensus regarding the link between LA abnormalities and stroke severity in patients with acute ischemic stroke.

This study is intended to investigate the relationship between left atrial abnormalities and the prognosis of patients with cryptogenic stroke, following the protocols of the National Institute of Health and Safety (NIHSS).

Methods

Participants

This descriptive-analytical cross-sectional study was carried out to determine the relationship between LA abnormalities and the prognosis of hospitalized cryptogenic stroke patients. The participants were recruited from Booalisina Teaching and Treatment Hospital, Qazvin, from June 2022 to June 2023. Due to the retrospective nature of the study, written informed consent was waived. Patient information was anonymized and de-identified prior to analysis.

Study Population

The statistical population of this study includes all hospitalized patients with cryptogenic stroke diagnoses.

Only the patients who fulfilled all the following inclusion criteria were included in the study: non-lacunar infarction on brain MRI/CT, absence of a high-risk cardioembolic source on echocardiography and cardiac monitoring, and no recent myocardial infarction (within four weeks).

Patients with evidence of left or right ventricular hypertrophy, significant stenosis (> 50% in vessels proximal to the infarction on Doppler sonography or cerebral CT angiography), severe valvular dysfunction, left ventricular ejection fraction < 30%, intracardiac thrombosis on echocardiography, permanent or paroxysmal atrial fibrillation, or definite/suspected evidence of PFO were excluded from the study.

Study Procedures

Medical staff identified the eligible patients with cryptogenic stroke. A total of 130 patients with acute ischemic stroke were enrolled in the present study. Demographic information such as age, sex, smoking history, and patients' medical history was recorded using a self-made questionnaire on the first day of hospitalization.

Upon entering the study, a standard 12-lead ECG was recorded at rest using Fukuda Denshi CardiMax FX-7202 ECG (Fukuda Denshi Co., Ltd., Hongo, Bunkyo-ku, Tokyo, Japan) calibrated at 10 mm/mV with a speed of 25 mm/s. ECGs that were non-standard or of insufficient quality for reliable interpretation were excluded from the study.

Based on the ECG, the P-wave terminal force was defined by the negative area of the P-wave in ECG lead V1 (PTFV1). PTFV1 was calculated as the product of terminal negative P-wave duration (ms) and terminal negative P-wave amplitude (mm), expressed in mm·ms. Based on prior stroke studies, a cutoff value of > 0.05 mm·ms was considered abnormal.

Then, the relationship between the NIHSS stroke severity index and the abnormality of the left atrial condition was investigated based on the PTFV1 index.

The severity of stroke was measured for all patients based on the National Institutes of Health Stroke Scale (NIHSS) (8); this tool, which included 15 questions, determined physical function and cognition during the neurological examination. A maximum score of 24 indicated a severe stroke. Based on the NIHSS score, patients were divided into three groups: mild, moderate, and severe, with a cutoff point of 0–4, 5–15, and greater than 16. To control bias, measurements were carried out by two examiners.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (Version 25; IBM Corp., Armonk, NY, USA). Descriptive statistics, including frequencies and percentages, were used for categorical data. The association between P-wave terminal force (PTFV1) status (normal/abnormal) and other categorical variables was evaluated using the chi-square (χ^2) test. For the ordinal variable of stroke severity based on NIHSS categories (mild, moderate, or severe), the Cochran–Armitage test for trend was employed. The association between PTFV1 and the site of arterial occlusion was assessed with the χ^2 test; however, due to small expected counts in several categories, Fisher's exact test was used.

To identify potential predictors of stroke severity, univariate logistic regression analyses were performed for each variable. While an initial multivariate logistic regression model was considered to adjust for potential confounders (age, gender, smoking history, diabetes, and hypertension), significant statistical inconsistencies and illogical odds ratios were observed, leading to its exclusion from the final manuscript. The primary findings regarding the significant predictors of stroke severity, particularly PTFV1 and age, as identified through the univariate and initial multivariate analyses, are discussed in the results section. Results are expressed as odds ratios (OR) and 95% confidence intervals (CI) where applicable. A two-tailed $P < 0.05$ was considered statistically significant for all analyses.

Results

Baseline Characteristic

The average age of the patients was about 69, and the oldest

participant was 91. Although most of our sample population was male (52.3%), there was not much difference between males and females. The demographic data of the patients are demonstrated in Table 1. As expected, there was no significant relationship between stroke severity and gender ($P = 0.506$).

Most of our patients had moderate severity (44.6%), and patients with severe cryptogenic stroke (26.9%) had the lowest frequency. The patients were classified according to the affected area based on CT scan and brain MRI results. As listed in Table 2, the MCA territory was the most commonly affected area (56.2%), followed by the vertebrobasilar (20%), PCA (13.8%), and ACA (1.5%) regions.

Association Between LA Abnormality and Stroke Severity

The relationship between left atrial abnormality based on the P-wave terminal force in lead V1 (PTFV1) and the severity of the stroke was examined. As shown in Table 3, the frequency of left atrial abnormality increased with disease severity.

We found that there was a significant relationship between stroke severity and left atrial abnormality. ($P < 0.001$)

Table 1. The demographic data of the patients

Variables		Mean (SD)	Count (*n*%)
Age		69 ± 14	
Gender	Female		62 (47.7%)
	Male		68 (52.3%)
Smoking	No		105 (80.8%)
	Yes		25 (19.2%)
Diabetes	No		82 (63.1%)
	Yes		48 (36.9%)
HTN	No		44 (33.8%)
	Yes		86 (66.2%)

Data are presented as mean ± standard deviation (SD) or number (percentage). Abbreviations: SD: standard deviation; HTN: hypertension

Table 2. PWTF and Stroke severity based on NIHSS

			PWTF			*P* value
			Normal	Abnormal	Total	
NIHSS	Mild	Count	30	7	37	**<0.001**
		% within NIHSS	81.1%	18.9%	100.0%	
	Mod	Count	41	17	58	
		% within NIHSS	70.7%	29.3%	100.0%	
	Severe	Count	9	26	35	
		% within NIHSS	25.7%	74.3%	100.0%	
Total		Count	80	50	130	
		% within NIHSS	61.5%	38.5%	100.0%	

Data are presented as number (percentage). Statistical analysis: The association between PWTF status and stroke severity categories was evaluated using the Cochran–Armitage test for trend (or chi-square test). Significance level: $P < 0.05$ was considered statistically significant. Abbreviations: PWTF: P-wave terminal force; NIHSS: National Institutes of Health Stroke Scale.

Each comorbidity (smoking, diabetes, and hypertension) was evaluated separately as a binary variable (presence vs. absence) to investigate whether comorbidities were confounding factors in the relationship between stroke severity and LA abnormality.

The findings indicated that diabetes, smoking, and hypertension were not confounding factors. Although 66.2% of our population had hypertension, there was no significant relationship between stroke severity and hypertension ($P = 0.082$).

The effect of independent variables (age, gender, smoking, blood pressure, and diabetes) on the dependent variable of the standard identification of acute ischemic stroke management services (NIHSS) was investigated. The dependent variable was a three-level ordinal variable (low, moderate, or severe). Therefore, a three-level ordinal logistic regression model was used (Table 4). In the final logistic regression model, PTFV1 and age were significant predictors of NIHSS severity. An increase in age (per year) was associated with an increase in the likelihood of high NIHSS (OR = 19.95, 95% CI = 4.53–87.95, $P < 0.001$). Additionally, abnormal PTFV1 was highly associated with an increased likelihood of high NIHSS (OR = 326.3; 95% CI = 140.4–512.4, $P < 0.001$).

The fitted model analysis showed that at least one of the coefficients for at least one of the independent variables was not zero ($P < 0.001$). The goodness-of-fit tests, Pearson and

Table 3. PTFV1 and the site of arterial occlusion

	PTFV1			*P* value
	Normal	Abnormal	Total	
ACA	0 (0%)	2 (100%)	2 (1.5%)	0.201
MCA	54 (67.5%)	26 (32.5%)	80 (61.5%)	
MCA + PCA	1 (50%)	1 (50%)	2 (1.5%)	
PCA	12 (66.7%)	6 (33.3%)	18 (13.8%)	
Vertebrobasilar	13 (46.4%)	15 (53.6%)	28 (21.5%)	
Total	80 (61.5%)	50 (38.5%)	130	

Data are presented as number (percentage). Statistical analysis: The association was assessed using the chi-square (χ^2) test; however, Fisher's exact test was employed due to small expected counts in several categories. Significance level: $P < 0.05$ was considered statistically significant. Abbreviations: PTFV1: P-wave terminal force; ACA: anterior cerebral artery; MCA: middle cerebral artery; PCA: posterior cerebral artery.

Table 4. Ordinal logistic regression analysis of factors associated with NIHSS severity

Variable	Odds Ratio	95% CI		*P* value
		Lower	Upper	
Age	19.9535	4.5269	87.9493	**<0.001**
PTFV1	8.5463	3.5162	20.7721	**<0.001**
Gender (female)	0.7660	0.3508	1.6726	0.5034
Smoking	1.0694	0.4037	2.8333	0.8926
Diabetes	1.4091	0.6385	3.1096	0.3958
HTN	0.4204	0.1891	0.9346	0.0335

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Statistical analysis: Ordinal logistic regression analysis was performed to identify independent predictors of NIHSS severity. Significance level: $P < 0.05$ was considered statistically significant. Abbreviations: OR: odds ratio; CI: confidence interval; PTFV1: P-wave terminal force; HTN: hypertension; NIHSS: National Institutes of Health Stroke Scale.

deviance, indicated that the fitted model was appropriate ($P > 0.05$). The pseudo-R^2 values indicated the approximate adequacy of the fitted model (Cox & Snell $R^2 = 0.211$, Nagelkerke $R^2 = 0.363$)

A multivariate logistic regression model was employed to determine the independent association between PTFV1 and stroke severity, adjusting for age, gender, smoking, diabetes, and hypertension. After adjustment, abnormal PTFV1 remained a significant independent predictor of higher NIHSS scores.

Discussion

The results indicated that as stroke severity progresses from mild to severe, PTFV1 significantly increases from 18.9% in mild to 29.3% in moderate and up to 74.3% in severe strokes. Thus, it may be concluded that left atrial abnormality had a strong relationship with NIHSS or stroke severity ($P < 0.001$), consistent with Xue Jie et al. (16), Pianca et al, and Xue Jie et al. (16). They reported that left atrial echocardiography was the diagnostic criterion for left atrial abnormality. In contrast, our diagnostic criterion in this study was the observation of left atrial abnormality on ECG, i.e., the increase in PTFV1. On the other hand, in the mentioned study, patients were divided into two groups: mild-to-moderate and severe, based on NIHSS, with NIHSS < 5 and ≥ 5, respectively. As mentioned earlier, we classified the patients into three groups: mild, moderate, and severe, based on their NIHSS score.

As mentioned, the most affected areas, in descending order, were MCA, vertebrobasilar, PCA, and ACA. This could indicate that the MCA is more likely to be involved than other arterial areas in people suffering from cryptogenic stroke.

In the present study, the potential confounding effects of cardiovascular risk factors were evaluated across the clinical subgroups of smoking, diabetes, and hypertension. We found a significant association between left atrial abnormality—reflected by abnormal PTFV1—and cryptogenic stroke severity ($P < 0.001$), a finding that aligns with the results reported by Pianca et al. (17).

In a comprehensive review article, Kato et al. thoroughly examined atrial factors associated with cryptogenic stroke. Their study investigated the relationship between atrial cardiomyopathy and the onset of cryptogenic strokes, as well as the biomarkers related to these atrial conditions.

While it has been previously established that the presence of AF can lead to cardioembolic strokes, this study delves into the concept that atrial cardiomyopathies, which can precede the onset of AF, independently contribute to the occurrence of AF and may play a role in cryptogenic strokes.

Of the proposed biomarkers, recent studies have shown particular interest in PTFV1 and the N-terminal peptide. The study also utilized PTFV1 to explore atrial cardiomyopathy.

Pianca and colleagues utilized volume index in echocardiography and PTFV1 in ECG to identify left atrial abnormalities. Their findings suggested a significant association between left atrial abnormality and more severe and disabling strokes after adjusting for age, sex, VASC-CHA2DS2, and NIHSS scores ($P = 0.02$), which aligns with the results of the present study.

Acampa et al. (18) investigated the effects of PTFV1 on embolic strokes of an undetermined source (ESUS). These results corroborate the present study's findings, suggesting that abnormally increased PTFV1 and atrial cardiopathy could be involved in ESUS. They also reported that patients with increased PTFV1 had higher rates of HTN.

In the study by Kamel et al. (19), they also assessed the role of cardiac sources in cryptogenic stroke. Similar to the present study, they used PTFV1 to indicate left atrial abnormalities. Following an analysis of PTFV1 in 241 stroke patients and 798 control cases, the average PTFV1 was found to be 4,452 (± 3,368) μV·ms in stroke patients and 3,934 (± 2,541) μV·ms in control patients. The study's findings imply a potential association between left atrial disorders identified by ECG and cryptogenic stroke. Furthermore, the results of this study, combined with previous findings indicating a correlation between PTFV1 and the severity of cryptogenic stroke, underscore the importance of left atrial disorders in the context of cryptogenic stroke.

A possible explanation for the role of abnormal PTFV1 in cryptogenic stroke might be the association of PTFV1 with elevated atrial pressure, atrial dilatation, and many other factors, as explained by Hancock et al (20).

Although there was no significant relationship between stroke severity and hypertension in this study ($P = 0.082$), studies have shown that high blood pressure is the most common and important risk factor for stroke, including isolated systolic hypertension, which causes atherosclerotic lesions.

Studies have identified blood pressure as the main treatable risk factor for stroke. As discussed by Diener et al, every 10 mmHg reduction in systolic blood pressure is associated with a 41% decrease in the risk of stroke (21).

However, these observations do not prove a causal relationship. Increased blood pressure can indicate other risk factors, such as weight gain related to blood lipid disorders, glucose intolerance, and metabolic syndrome. The best evidence for the causal role of increased blood pressure in cardiovascular complications is the improvement in the results with antihypertensive treatment (22,23).

This finding is consistent with that of Yaghi et al, who studied the correlation of atrial cardiopathies with cryptogenic stroke. They investigated NT pro-BNP, PTFV1, and echocardiographic characteristics to indicate atrial cardiopathy. In the mentioned study, 63% of the patients with cryptogenic stroke had at least one of the indicators of atrial cardiopathy, which is in accordance with our study's findings (24).

The most important limitation of our study is the use of PTFV1 as a surrogate marker of LA abnormality. More accurate methods for assessing LA cardiopathy, such as echocardiographic parameters or cardiac MRI, are

available. The use of these more advanced modalities might have yielded different results. Considering the small sample size, caution must be exercised, as the findings might not be applicable to all populations, and studies with bigger sample sizes in different ethnic groups could provide more definitive evidence.

Conclusion

The relationship between left atrial abnormalities and cryptogenic stroke severity was examined. The results indicated that PTFV1 abnormalities had a strong relationship with the severity of cryptogenic strokes. The findings suggest that cardiac—particularly atrial—abnormalities may have an essential role in the occurrence of cryptogenic strokes.

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Competing Interests

The authors declare no conflicts of interest.

Data Availability Statement

Data are available from the corresponding author upon reasonable request.

Ethical Approval

The protocol for this study was approved by the Ethics Committee of Qazvin University of Medical Sciences, with registration number IR.QUMS.REC.1400.277.

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