

Assessment of Clinical Outcomes After Percutaneous Patent Foramen Ovale Closure In Adult Patients Diagnosed With Cryptogenic Stroke

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ABSTRACT

Our study aims to report the findings of transesophageal echocardiography (TEE), Risk of Paradoxical Embolism (RoPE) score, the Patent Foramen Ovale -Associated Stroke Causal Likelihood (PASCAL) classification analyses, and follow-up results after percutaneous PFO closure in patients diagnosed with cryptogenic stroke.

The medical records of patients with acute arterial ischemic stroke who were diagnosed with PFO by TEE and applied percutaneous PFO closure between 2020-2023 were reviewed. The echocardiography (Echo) score, the RoPE score, and the PASCAL classification were calculated for all patients as indicated in the literature. Newly developed arrhythmia, recurrent stroke, and cardiovascular death were recorded during follow-up.

A total of 65 patients were included in the study. The median age was 41 years [range:33-47]), the median RoPE score was 8, and the Echo score was 3. While 29.2% of the patients were in the possible group according to the PASCAL classification, 70.8% were in the probable group. We did not have any patients in the unlikely group. Recurrent ischemic stroke was detected in only two patients at a median follow-up of 12.1 months. No cardiac arrhythmia or cardiovascular death was observed.

PFO closure in PFO-associated stroke patients was safe, with a low incidence of arrhythmia and cardiovascular and cerebrovascular events during the short-term follow-up.

Keywords: Embolism, paradoxical, ischemic stroke, transesophageal, echocardiography

Introduction

The definition of cryptogenic stroke was classified as a stroke of unknown origin and had a frequency of 40% before technological developments (1). However, with the advancing imaging techniques, this rate decreased to 15-30% (1,2). PFO is frequently found in 25% of the healthy population without clinical signs (2). Patients with an ischemic stroke-associated patent foramen ovale (PFO) should undergo a comprehensive evaluation to ensure that the causes of ischemic stroke are the most likely stroke mechanism associated with PFO (3). The most commonly used system to determine the PFO-associated ischemic stroke risk; is the Risk of Paradoxical Embolism (RoPE) scoring system, including patient age, classic risk factors, and infarct type(4).

However, more comprehensive scoring was needed because the RoPE score did not include the anatomical high-risk features of PFO and the stroke recurrence rates were lower in patients with a higher RoPE Score (6). In contrast, the PFO-Associated Stroke Causal Probability (PASCAL) classification system includes PFO anatomical components and clinical characteristics of patients (including shunt size, absence or presence of atrial septal aneurysm (ASA), and/or venous thromboembolism) in addition to the RoPE score) (7).

PFO closure has been suggested as a prospective treatment to lower the risk of PFO-associated stroke by obstructing the passage of emboli from the venous to the arterial circulation. Numerous trials have been executed to investigate the effectiveness and safety of PFO closure in comparison to medical therapy

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among patients with PFO-associated stroke (8,9). However, these studies have yielded conflicting results, leading to an ongoing debate and uncertainty surrounding the use of PFO closure as a treatment for PFO-associated stroke.

In this study, we aimed to add to the literature our experience according to echocardiographic data and stroke-related patent PFO scoring systems in patients admitted for PFO closure and follow-up in our center. Newly developed arrhythmia, recurrent stroke and cardiovascular death were recorded and the results were shared.

Materials and Methods

The study is a single-center study and retrospective that included the patients who underwent percutaneous PFO closure and were referred to our center due to cryptogenic stroke by the Neurology Clinic between March 2020 and July 2023. We included patients over 18 years old who met the criteria for high-risk PFO on transesophageal echocardiography (TEE). Patients who failed to fulfil the criteria for cryptogenic stroke (10) and who met at least one of the following criteria were excluded; atrial fibrillation, atrial flutter, atrioventricular and interventricular block, pacemaker rhythm, severe valve dysfunction, segmental movement disorder, mechanical prosthetic valve. Patients' demographic, laboratory and clinical characteristics were obtained from the hospital automation system. The study followed the ethical principles outlined in the Declaration of Helsinki and received approval from the local ethics committee (June 2023 dated 2023-06-234).

Definitions and Risk Factors: The study collected data on various patient factors, including age, smoking status, and comorbidities such as hypertension (HT), and diabetes mellitus (DM). To determine the presence of DM, patients were classified as positive if they met any of the following criteria: they were using blood glucose-lowering medications, had fasting plasma blood glucose levels ≥ 126 mg/dL, or had postprandial blood glucose levels ≥ 200 mg/dL. Hypertension (HT) was defined as having a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or if patients were on antihypertensive medication (11).

Ischemic stroke was characterized as a sudden focal neurological deficit persisting for a minimum of 24 hours or more, or when correlated with an associated infarction observed on brain magnetic resonance imaging. The definition of cryptogenic stroke included an extensive search to exclude other identifiable strokes mechanisms such as large artery

atherosclerotic disease (defined with a stenosis of at least 50% or more in a main vessel), lacunar stroke (defined by small deep infarction) a confirmed cardioembolic source, small vessel disease, hypercoagulation disorder, or vessel dissection. All patients in the study underwent noninvasive angiographic and ultrasonographic imaging to exclude the possibility of stroke of vascular origin. Holter was performed to exclude paroxysmal atrial fibrillation.

Transesophageal Echocardiography Analysis and Scoring:

The present study utilized a standardized TEE protocol to evaluate the atrial septum's morphological characteristics and the existence of a high-risk PFO, which permits blood flow between the right and left atria of the heart. This examination was performed under resting conditions and during the Valsalva maneuver, a forced expiratory effort (11). High-risk PFO was characterized by the presence of any of the following morphological features: PFO with an associated atrial septal aneurysm (ASA) (defined as having an excursion ≥ 10 mm from the midline), PFO length greater than 10 mm, PFO width exceeding 2 mm, a significant right-to-left (RL) shunt at rest or during the Valsalva maneuver (defined as >20 bubbles in the left atrium in the first three cycles of TEE) (12), and the presence of a Chiari network or Eustachian valve. All images were interpreted after scanning by two experienced cardiologists who were unaware of the patient's characteristics and study design. A score was given for each High-risk PFO factor, and these scores were summed to calculate the total echocardiography score (13,14). RoPE scoring and PASCAL classification. RoPE scoring is determined by calculating demographic (age, DM, HT, smoking, history of transient ischemic attack or stroke and cortical imaging criteria (large [>1 to 1.5cm] and superficial). PASCAL classification is made by adding the RoPE score and the large shunt and ASA findings detected in TEE (7) (Table 1).

Statistical Analysis: The study data were analyzed using descriptive statistics. Continuous variables were reported as median [interquartile range (IQR)]. Categorical variables were presented as counts (n) and percentages (%). The participants were divided into two groups based on RoPE groups, and the Mann-Whitney U-test was employed for continuous variables. The Chi-square test was utilized for the comparison of categorical variables between the two groups. The statistical significance was considered at a p-value of less than 0.05. The Statistical Package for the Social Sciences (SPSS version 22.0, SPSS Inc., Chicago, IL, USA) was used for conducting these statistical assessments.

Results

A total of 65 cryptogenic stroke patients with PFO closure were included in the study (Median age [IQR]: 41 [33-47]). Of the study population, 50.7% were male, 27.6% were diabetic, 32.3% were hypertensive, 41.5% were smokers and 18.4% had CAD. TEE revealed a Chiari network in 20%, a Eustachian valve in 9.2% and Lipomatous hypertrophy in 7.7% of the patients. Large RL shunt (89.2%) and ASA (61.5%) were the most common echocardiographic high-risk criteria. The median PFO tunnel length was 12 mm [IQR (8.9-16)] and the tunnel width was 5 mm [IQR (4-7.2)] on the mid-esophageal 70-90 degree images. The Median RoPE score was 8 and the echocardiography score was 3 (Table 2). While 29.2% of the patients were in the possible group according to the PASCAL classification, 70.8% were in the probable group and no patients were in the unlikely group (Table 3). Procedural failure was detected in only one patient. Recurrent ischemic stroke and rehospitalization were seen in only two patients at a mean follow-up of 12.1 months. No cardiac complications or arrhythmia were observed.

Discussion

This study demonstrated that percutaneous closure of PFO in patients with PFO-associated stroke is reliable and associated with a low risk of recurrent stroke during follow-up, consistent with current scientific literature. The patients included in the study had high RoPE scores and were mostly classified as having a possible PFO-related stroke according to the PASCAL criteria. The low rates of recurrent ischemic stroke and hospitalization further reinforced the effectiveness of the procedure.

In individuals with PFO, stroke can occur through a PFO-associated mechanism (e.g., paradoxical embolism) or another hidden mechanism (such as large artery atherosclerosis, minimal stenotic cervical-cerebral atherosclerotic plaque, cardioembolism, small vessel disease, paroxysmal atrial fibrillation, or others)(15,16,17). Therefore, whether PFO is related to stroke in patients with SVO is still a matter of research and debate. There are many studies on this subject, but there is no clear consensus^(9,18). Because of the lack of consensus, clinicians have difficulty in making decisions. Scoring systems guide the clinician in terms of patient benefit. One of the most widely accepted scoring systems for this is the RoPE score. However, a significant limitation of the RoPE Score is that it does not take into account certain high-risk

PFO (like ASA and large RL shunt combination) anatomical characteristics. Several studies have demonstrated a strong association between PFO with ASA and RL shunt and the risk of recurrent ischemic cerebrovascular events. The presence of an ASA and a large RL shunt increases the likelihood of PFO-associated stroke due to an increase in the volume and pressure of the RL shunt. The risk of recurrent ischemic cerebrovascular events in patients with PFO, ASA, and large RL shunt can be up to four times higher than in patients with PFO alone (19,20). In a recent study, the limitations of the RoPE Score were addressed by incorporating additional factors indicating a high risk of PFO, such as the presence of ASA, and large RL shunt (6,7). This approach is known as the PASCAL classification system, which solves the constraint of the RoPE Score by merging its information with PFO functional and structural elements. These elements are physiologically hypothesized and epidemiologically shown to exacerbate PFO stroke risk, specifically shunt size and the presence of an ASA. By incorporating these additional factors, the PASCAL classification system provides a more comprehensive and accurate assessment of stroke risk in patients with PFO⁽⁷⁾. As per the findings reported by Kent et al., approximately 15% of patients in the PASCAL unlikely categorization who lacked a high-risk PFO and also had vascular risk factors did not seem to experience any benefit with device closure. On the contrary, device closure was linked with nearly a 90% relative risk decrease in patients with a PASCAL probably categorization who had both high-risk PFO features and a high RoPE Score⁽⁷⁾. In our study, 29.2% of the patients who underwent PFO closure were in the possible group according to the PASCAL classification, and 70.8% were in the probable group. We did not have any patients in the unlikely group. Moreover, patients with PFO closure in our study population met the criteria for anatomic high risk at higher rates than patients with PFO closure in this trial, which included endpoint analyses of 6 pivotal studies (7) (89.2% of patients had large RL shunts and 61.5% ASA). Of course, the median RoPE score in our study was similarly high to the median RoPE score in patients undergoing device closure as found in these pivotal studies.

There are large studies, including RESPECT, REDUCE, DEFENS-PFO, and CLOSE trials, investigating the efficacy and safety of PFO closure compared to medical treatment for the prevention of recurrent stroke in patients with cryptogenic stroke and high-risk PFO. A meta-analysis of these large studies revealed that the PFO closure procedure was superior to medical follow-up (21). The risk of

Table 1. Risk of Paradoxical Embolism Score and PFO-Associated Stroke Causal Likelihood Classification System

Variable	points	
RoPE score Calculator		
No history of		
Hypertension	+1	
Diabetes Mellitus	+1	
Stroke or TIA	+1	
Nonsmoker	+1	
Cortical infarct on imaging	+1	
Age		
18-29	+5	
30-39	+4	
40-49	+3	
50-59	+2	
60-69	+1	
≥70	0	
Total RoPE Score	10	
PASCAL Classification System		
High RoPE score (≥7)	LS and/or ASA	PFO-associated stroke
Absent	Absent	Unlikely
Absent	Present	Possible
Present	Absent	
Present	Present	Probable

Abbreviation: ASA, atrial septal aneurysm; LS, large shunt; PFO, patent foramen ovale; PFO-Associated Stroke Causal Likelihood Classification (PASCAL); RoPE, Risk of Paradoxical Embolism; TIA, trans ischemic attack. and

subsequent stroke in patients receiving medical treatment was approximately 1% annually, which decreased by almost 60% with PFO closure (22). In this meta-analysis(14) and similar studies, newly developed AF was identified as the most common complication associated with the PFO closure procedure, with an increased risk of 4.7%. However, because AF is self-limiting, no increased embolic risk has been reported(22,23). Although the patient population was small in our study, only 2 patients had recurrent strokes after PFO closure, and no AF development or procedure-related complication was observed during the follow-up period. These results confirmed the procedure's relative safety, the limitations of its mid-term adverse effects, and the obvious benefits.

Limitation: Our study has several noteworthy limitations that should be considered. Firstly, it is important to note that this study was conducted retrospectively at a single-center, which may limit the generalizability of the findings. Secondly, the sample size was small, and the absence of a control group further reduced the strength of our conclusions. Thirdly, the study population comprised young individuals who lacked several traditional vascular risk

factors such as DM, HT, and smoking. Consequently, the study population had high RoPE scores and was predominantly classified in the probable PFO-associated stroke group according to the PASCAL classification. This limits our ability to examine the effectiveness of PFO closure in the middle to advanced age group, which is believed to be at low risk based on RoPE scoring but at high risk based on echocardiographic findings. Fourthly, the absence of long-term patient follow-up data restricts our ability to comment on the long-term benefits of PFO closure.

In this study, we report a single-center experience of PFO closure in PFO-associated stroke patients. PFO closure was safe, with a low incidence of arrhythmia and cardiovascular and cerebrovascular events during the short-term follow-up. However, further research with larger sample sizes, prospective designs, longer follow-up periods, and diverse patient populations is needed to establish more definitive conclusions regarding the effectiveness and long-term benefits of PFO closure.

Ethics Committee Approval: The study was conducted following the ethical principles stated in

Table 2. Baseline Characteristics of The Study Population

Age, years, [IQR]	38 [33-44]	42.5 [33.5-51.2]	41 [33-47]	0.152
Diabetes Mellitus, n (%)	11 (33.3)	6 (18.8)	17 (26.2)	0.181
Hypertension, n (%)	11 (33.3)	10 (31.2)	21 (32.3)	0.857
Smoking, n (%)	10 (30.3)	19 (59.4)	29 (44.6)	0.018
CAD, n (%)	3 (9.1)	7 (21.9)	10 (15.4)	0.153
RoPE score, [IQR]	8 [6.5-9]	7 [6-8]	8 [6-9]	0.182
Echo score, [IQR]	3 [2-4]	3 [2-4]	3 [2-5]	0.899
Echocardiographic Features				
Chiari network, n (%)	7 (21.2)	6 (18.8)	13 (20)	0.804
Eustachian valve, n (%)	4 (12.1)	2 (6.2)	6 (9.2)	0.414
Atrial septal aneurysm, n (%)	19 (57.6)	21 (65.6)	40 (61.5)	0.505
Large RL shunt, n (%)	29 (87.9)	29 (90.6)	58 (89.2)	0.721
Lipomatous hypertrophy, n (%)	1 (3.0)	4 (12.5)	5 (7.7)	0.152
PFO length, mm, [IQR]	12 [8.5-15.6]	12.5 [8.9-16.7]	12 [8.9-16]	0.520
PFO width, mm, [IQR]	5 [4-7.5]	5 [4.3-7.3]	5 [4-7.2]	0.833
Procedure				
Complication,(n)				
Vascular death	0	0	0	
Composite stroke	0	0	0	
Bleeding	0	0	0	
Arrhythmias	0	0	0	
Failed attempted	0	1	1	
MACE, (n)				
Arrhythmias	0	0	0	
Rehospitalization	2	0	2	
Recurrent CVE	2	0	2	
Hemorrhagic CVE	0	0	0	

Values are presented as numbers (n) and percentages (%), median (interquartile range 25th-75th percentiles). For continuous data, the p-value was calculated using the Mann-Whitney U-test, and for categorical variables, the Chi-Square test or Fisher's exact test, as appropriate.

p<0.05 was considered statistically significant. **Abbreviation:** CAD, coronary artery disease; CVE, cerebrovascular event; Echo, echocardiography; IQR; interquartile range, RL; right to left, MACE, major adverse cardiac events; PFO, patent foramen ovale; RoPE, Risk of Paradoxical Embolism Score

Table 3. Risk of Paradoxical Embolism Score (RoPE) and PFO-Associated Stroke Causal Likelihood Classification (PASCAL) System's results

	RoPE score	PASCAL classification system		
	High (≥ 7)	Unlikely	Possible	Probable
Device closure, n(%)	43 (66.1)	-	19 (29.2)	46 (70.8)

the Declaration of Helsinki and was approved by the local ethics committee (April 2022 dated 2022-04-109).

Informed Consent: The necessity for obtaining a written informed consent form from every participant was waived, owing to the retrospective design of the

study.

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Conflict of Interest: The authors affirm that there are no conflicts of interest to report.

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