Original Article

Percutaneous Patent Foramen Ovale Occlusion in Patients Over 60 Years of Age with History of Stroke

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Abstract

Background: The prevalence of patent foramen ovale (PFO) is 27%. PFO is related to paradoxical embolism, which can cause ischemic stroke. Ischemic stroke without an identifiable cause is common, accounting for up to 40% of cases, and PFO is frequently found in these patients. The prevalence of PFO is almost 3 times higher in elderly patients with ischemic stroke without identified etiology, suggesting that these patients may also benefit from PFO closure.

Objectives: The primary objective was to assess the recurrence of ischemic stroke or transient ischemic attack during clinical follow-up. The secondary objective was to assess the occurrence of procedural complications, onset of atrial fibrillation, and reduced anticoagulant use.

Methods: This retrospective cohort study included 36 patients over 60 years of age with prior ischemic stroke who underwent PFO closure. Survival analysis was performed using the Kaplan-Meier model. Independence tests between categorical variables were performed using the chi-square test and Fisher's exact test, adopting a significance level of 0.05.

Results: The patients' mean age was 69.6 ± 6.5 years, and 55.5% were men. No complications occurred during the procedures. Echocardiography was performed 30 days after the intervention, showing no residual shunts. During the follow-up of 58.9 ± 42.7 months, there were no cases of ischemic stroke, transient ischemic attack, or atrial fibrillation related to the procedure. The use of anticoagulants decreased from 41.7% to 5.6% (p = 0.03).

Conclusions: Percutaneous PFO occlusion for the prevention of cerebrovascular events in individuals over 60 years of age with prior ischemic stroke is effective and safe, with a low risk of complications, and it can reduce the risk of bleeding by reducing the use of anticoagulants.

Introduction

The foramen ovale is an important component of circulation during fetal development, spontaneously occluding in the majority of people after birth.[1] The prevalence of patent foramen ovale (PFO), derived from autopsy, is approximately 27%, but it decreases with advancing age; after 80 years of age, it is found in 20% of the population.[2] Another relevant aspect refers to the concept of paradoxical embolism, first described in 1877,[3] confirmed by a high incidence of ischemic stroke in patients with PFO.[4] In this sense, the term cryptogenic ischemic stroke is characterized by a cerebral infarction whose origin cannot be attributed to specific causes, for example, intracavitary cardiac thrombi, atherosclerosis of the large arteries, small vessel disease, or other known etiologies. However, even after extensive clinical assessment, approximately 25% to 40% of patients with cerebrovascular ischemia do not present a specific cause, and PFO is a common condition in these cases.[5] Current interest in the topic increased after a 1988 study by Lechat et al.,[6] who observed the presence of PFO in 40% of patients with ischemic stroke, in comparison with only 10% in control groups. Subsequently, further studies highlighted the association of PFO in patients with ischemic stroke, especially in individuals under 55 years of age.[7] The prevalence of PFO is almost 3 times higher in elderly patients with cryptogenic ischemic stroke in comparison with age-matched patients with a known cause of ischemic stroke, suggesting that elderly patients may benefit from PFO closure.[8]

Therefore, the primary objective of this study was to assess the recurrence of ischemic stroke or transient ischemic attack in the clinical follow-up of patients over 60 years of age with prior ischemic stroke who underwent PFO closure. The secondary objective was to assess the occurrence of complications related to the procedure and the emergence of atrial fibrillation after the intervention.

Keywords

Patent Foramen Ovale; Ischemic Stroke; Percutaneous Occlusion; Aged; Stroke

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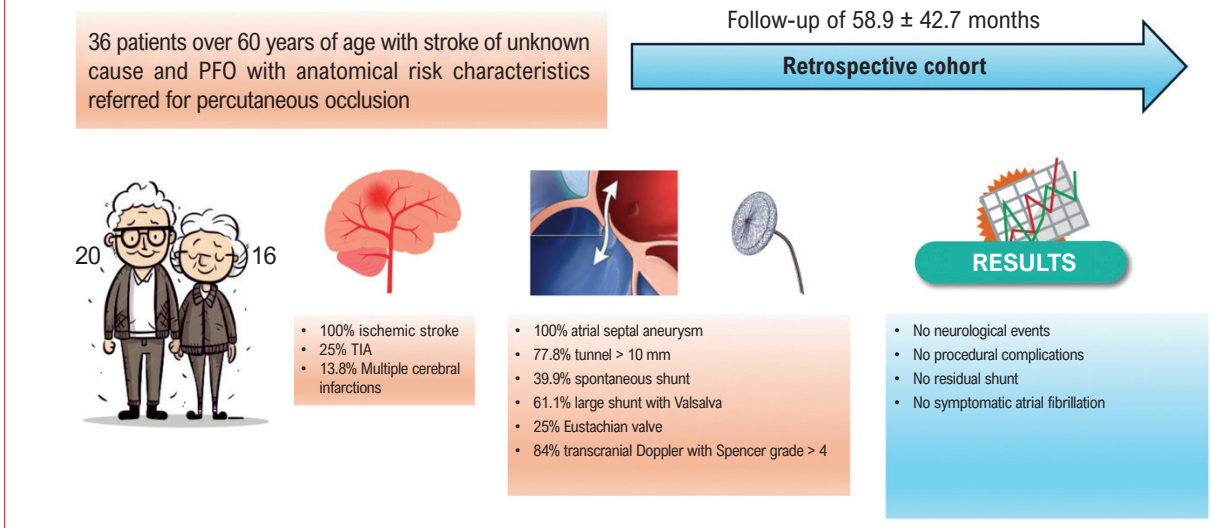
Central Illustration: Percutaneous PFO occlusion in patients over 60 years of age with history of stroke



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TIA: transient ischemic attack; PFO: patent foramen ovale.

Methods

This retrospective cohort study was carried out at the Hospital Unimed Nordeste do Rio Grande do Sul, Brazil, including patients over 60 years of age, with prior ischemic stroke, who underwent percutaneous PFO occlusion to prevent new cerebrovascular events between March 2019 and January 2024.

Initially, it is worth highlighting that the characterization of PFO-related ischemic stroke was defined in the absence of other possible causes of ischemic stroke, for example, significant atherosclerosis in large arteries, small artery atherosclerosis (lacunar infarctions), important probability of cardiac embolization (atrial fibrillation, cavitary thrombi), and infrequent causes of ischemic stroke (arterial dissections, arteritis). Accordingly, these conditions were excluded in all patients with 24-hour Holter monitoring, cranial computed tomography angiography, Doppler ultrasound of the carotid and vertebral arteries, transesophageal echocardiography, and brain magnetic resonance imaging. The diagnosis of stroke and its association with PFO were assessed by the hospital's neurologists. Patients with a PFO-Associated Stroke Causal Likelihood (PASCAL) score classified as probable or possible to indicate the relationship between the event and PFO were considered for inclusion.[9]

PFO was diagnosed by transesophageal echocardiography. The study considered patients with high-risk anatomy, characterized by interatrial septal aneurysm (defined as an excursion of 10 mm to one side or 15 mm adding the excursion between the right and left atrium), spontaneous shunt or large shunt with Valsalva maneuver (grade 3, more than 20 bubbles through the PFO), and transcranial Doppler with Spencer grade equal to or greater than 3.[10] All patients met the criteria put forth by Nakayama for identifying high-risk anatomy.[11]

The decision to perform the procedure was made by a multidisciplinary team involving cardiology, neurology, patients, and family members, with informed consent in accordance with hospital criteria.

Percutaneous occlusion was performed under general anesthesia or local anesthesia with sedation, according to anesthetic assessment. Three-dimensional transesophageal ultrasound and radioscopy were used in all procedures, performed by a team including an interventional cardiologist, echocardiographer, and anesthesiologist. Prosthesis size was chosen based on the anatomical characteristics of the foramen ovale, adjacent structures, and echocardiographic measurements, using 2 device types: Memopart PFO™ (Lepu Medical Technology, China) and Cocoon PFO Occluder™ (Sahajanand Medical Technologies, India).

Clinical assessment was performed 30 days after the procedure with a control transthoracic echocardiogram. Follow-up with the interventional team was carried out by telephone contact at 6 months, 12 months, and annually thereafter.

Before the procedure, a protocol infusion of 2 g of intravenous cefazolin was performed, completing 3 doses with an 8-hour interval for all patients. Additionally, anticoagulants were suspended in patients who were using them, according to the individual protocol, and dual antiplatelet therapy with acetylsalicylic acid 100 mg/day and clopidogrel 75 mg/day

was initiated, with a recommendation to continue for 6 months after the procedure. In patients with an indication for anticoagulation, it was maintained after the procedure. It is worth highlighting that the attending physician had complete freedom to adjust antiplatelet and anticoagulant medications according to patients' clinical indications.

Based on resolution 466/12 of the Brazilian National Health Council (CNS, acronym in Portuguese), which approves the regulatory standards and guidelines for research involving human beings, this research project was submitted to the Research Ethics Committee of the University of Caxias do Sul (UCS). A waiver of the informed consent form was requested, because the research was restricted to consulting medical records, without including patients' names or any other characteristics that individualize patients. A data use agreement was signed, guaranteeing the confidentiality of the information studied by the researchers. The Bioethics and Research Committee of the Hospital Unimed Nordeste do Rio Grande do Sul provided us with a letter of consent for the proposed study.

The inclusion criteria were patients over 60 years of age who underwent percutaneous PFO occlusion due to ischemic stroke of unknown cause and foramen ovale anatomy with risk of paradoxical embolism (RoPE). Patients were excluded if they were under 60 years of age, had other probable causes of ischemic stroke, or did not have foramen ovale anatomy with RoPE.

Statistical analysis

For the statistical analysis section, we conducted a series of procedures in R software, version 4.4.1. We used measures of central tendency (mean and median), as well as measures of dispersion (standard deviation and interquartile range) to describe the numerical variables. For categorical variables, frequencies and percentages were calculated. The bootstrap technique was also applied to estimate the confidence interval for the median of patients' follow-up times. Using 2000 replications, this nonparametric approach allowed us to obtain a 95% confidence interval for the median, an important central measure for assessing follow-up time.

Another relevant aspect is survival analysis, which was conducted using the Kaplan-Meier model, a method for estimating the survival function based on time-to-event data. We complemented this analysis by visualizing survival curves using the Survminer package, which facilitates interpretation by including elements such as the risk table, the confidence interval of survival estimates, and the median survival line. We performed independence tests between categorical variables using the chi-square test and Fisher's exact test. These analyses allowed us to investigate possible associations between different categorical variables, for example, stroke prevention strategies and brands of prostheses used. Adjustments for multiple comparisons were carried out using Monte Carlo simulations in order to ensure the statistical accuracy of the results.

A significance level of 0.05 was adopted for all statistical analyses. To avoid type I errors resulting from multiple comparisons, we used the Bonferroni-Holm adjustment method, seeing that it increases the reliability of the results, minimizing the chance of false positives and strengthening the robustness of our conclusions.

Results

Table 1 summarizes the patient characteristics, highlighting that the mean age was 69.6 ± 6.5 years, and 55.5% of the patients were male. The prevalences of arterial hypertension, diabetes mellitus, and dyslipidemia were 27%, 22.2%, and 41.6%, respectively; none of the patients included in the study were current smokers. In addition to ischemic stroke, 9% of the patients also had associated transient ischemic attacks, and 13.8% had multiple cerebral infarctions. Table 2 describes the anatomical characteristics of the PFO. Atrial septal aneurysm was found in all patients. A tunnel with more than 10 mm in length in the PFO was found in 77.8%. Spontaneous right-to-left shunt was found in 38.9%, and the other 61.1% had significant shunt with Valsalva maneuver. Furthermore, additional risk characteristics such as Eustachian valve and Chiari network were found in 25% and 8.3%, respectively. All patients underwent transcranial Doppler, and significant flow (Spencer grade equal to or greater than 4) was found in 84.5% of patients.

Table 3 summarizes the procedure details. General anesthesia was performed in 72.2% of cases, and the remaining patients underwent sedation and local anesthesia. Two device types were used: Memopart PFO™ (Lepu Medical Technology, China) in 69.5% of patients and Cocoon PFO Occluder™ (Sahajanand Medical Technologies, India) in the other 30.5%. Regarding size, 47.3% of patients used 24- or 25-mm prostheses; 49.9% used 28- and 30-mm prostheses, and 1 patient used a 34-mm prosthesis. It is worth underscoring that the procedure was successful in all patients, and no major complications occurred. Hospital stay was 22.9 ± 1.6 hours.

Tables 4 and 5 summarize the characteristics of clinical follow-up. Before the procedure, 41.6% of patients were using non-coumarin anticoagulants, and 58.4% of patients were using antiplatelet agents; of these, 44.5% were using dual antiplatelet therapy. As per protocol, during and 6 months after the procedure, 94.4% of patients remained on dual antiplatelet therapy, and 5.6% remained on anticoagulation as recommended by the attending physician. After 6 months, medication was adjusted in accordance with clinical criteria. It is worth highlighting that anticoagulants were reduced in 86.6% ($p = 0.03$), being used in only 5.6% of the patients. In relation to other medications, 88.8% continued with an antiplatelet agent (83.2% with acetylsalicylic acid and 5.6% with clopidogrel), and 5.6% did not receive antiplatelet agents or anticoagulants. A control echocardiogram was performed in all patients 30 days after the procedure, and no residual shunt was found in any of them. During the follow-up period, no patient had ischemic stroke or transient ischemic attack. Only 1 patient had a hemorrhagic stroke 2 years after the procedure, therefore unrelated to the intervention; he had been using acetylsalicylic acid alone for secondary prevention of ischemic stroke. There were no complications related to the prosthesis, and 1 patient developed atrial fibrillation 1 year after the procedure, therefore, also not associated with

Table 1 – Patient characteristics

Clinical characteristics	n = 36
Age (years)	69.6 ± 6.5
60 to 69 years (%)	15 (41.6%)
70 to 79 years (%)	18 (50%)
80 to 89 years (%)	3 (8.4%)
Male sex (%)	20 (55.5%)
Clinical follow-up (months)	58.9 ± 42.7
Arterial hypertension (%)	10 (27%)
Diabetes mellitus (%)	8 (22.2%)
Dyslipidemia (%)	15 (41.6%)
Current smoking (%)	0
Cerebrovascular events	
Ischemic stroke (%)	36 (100%)
TIA (%)	9 (25%)
Multiple cerebral infarctions (%)	5 (13.8%)
Bleeding score	
HAS-BLED 1 (annual risk of bleeding 1.02%)*	9 (25%)
HAS-BLED 2 (annual risk of bleeding 1.88%)	20 (55.5%)
HAS-BLED 3 (annual risk of bleeding 3.74%)	7 (19.5%)

*TIA: transient ischemic attack. *Pisters et al.[12]*

Table 2 – PFO characteristics

	n = 36
Interatrial septal aneurysm (%)	36 (100%)
Tunnel ≥ 10 mm (%)	28 (77.8%)
Spontaneous right-to-left shunt (%)	14 (38.9%)
Grade 3 shunt with Valsalva (%)	22 (61.1%)
Eustachian valve (%)	9 (25%)
Chiari network (%)	3 (8.3%)
Transcranial Doppler, Spencer grade ≥ 4	34 (84.5%)

Table 3 – Procedure characteristics

	n = 36
General anesthesia (%)	26 (72.2)
Local anesthesia + sedation (%)	10 (27.8)
3D transesophageal echocardiography (%)	36 (100)
Device type	
Lepu (%)	25 (69.5)
Cocoon (%)	11 (30.5)
Device size (mm)	
24 (%)	13 (36.1)
25 (%)	4 (11.2)
28 (%)	11 (30.5)
30 (%)	7 (19.4)
34 (%)	1 (2.8)
Procedure success (%)	36 (100)
Major complications (%)	0 (0)
Duration of hospital stay (hours)	22.9 ±1.6

Table 4 – Medications before and after the procedure

	Before	6 m	After 6 m
Anticoagulants	15 (41.6)	2 (5.6)	2 (5.6)*
Rivaroxaban	5 (13.9)	1(2.8)	0
Apixaban	3 (8.4)	1 (2.8)	1 (2.8)
Dabigatran	7 (19.3)	0	1 (2.8)
Antiplatelet agents	21(58.4)	34 (94.4)	32 (88.8)
ASA	5 (13.9)	0	30 (83.4)
Clopidogrel	0	0	2 (5.6)
ASA + clopidogrel	16 (44.5)	34 (94.4)	0
None	0	0	2 (5.6)

*ASA: acetylsalicylic acid; m: months. *86.6% reduction (p = 0.03), as assessed by the chi-square test with bootstrap analysis.*

PFO closure. No patient died during the follow-up period. The Kaplan-Meier plot (Figure 1) illustrates the probability of survival after endovascular PFO closure in elderly patients with a history of stroke. The survival curve line remains close to 1.00 throughout the follow-up period of up to 150 months, indicating an elevated and sustained survival rate over time. The risk table below the plot shows the number of patients at risk at specific time intervals, starting with 36 patients and declining to 1 at the end of the follow-up period. The stability of the curve suggests that the endovascular closure procedure may be associated with a favorable long-term prognosis in preventing subsequent adverse events in a vulnerable elderly population, considering the patients' clinical context and health variables. Kaplan-Meier analysis serves as a valuable

Table 5 – Clinical results after PFO occlusion

	n = 36
30-day control echocardiogram (%)	36 (100%)
Residual shunt (%)	0
Clinical follow-up (months):	58.9 ±42.7
Ischemic stroke (%)	0
Transient ischemic attack (%)	0
Hemorrhagic stroke (%)	1 (2.8%)
Prosthesis-related complications (%)	0
Detection of atrial fibrillation (%)	1 (2.8%)
Survival (%)	36 (100%)

tool to evaluate the effectiveness of medical interventions over time, and, in this case, indicates a positive treatment outcome.

Discussion

In this study, there were no recurrences of ischemic neurological events, onset of atrial fibrillation, or prosthesis-related complications during clinical follow-up.

It is known that the prevalence of PFO is almost 3 times higher in elderly patients with cryptogenic stroke in comparison with age-matched patients with a known cause of stroke, suggesting that elderly patients may benefit from PFO closure.[8,12]

Although the RESPECT-LT, CLOSE, and REDUCE trials[13-15] have established the superiority of PFO closure versus medical therapy for the prevention of recurrent ischemic stroke, none of them included patients over 60 years of age. Although no randomized clinical trials have been conducted comparing patients over 60 years of age with PFO closure versus medical therapy, some recent small studies have suggested that PFO closure in elderly patients is safe and may decrease the risk of recurrent stroke.[16-18]

The DEFENSE-PFO trial included patients over 55 years of age and demonstrated positive results for PFO closure compared with medical therapy alone, although the mean age was only 51.8 years, and there were 120 patients with 2 years of follow-up. The results support PFO closure rather than medical therapy in middle-aged patients with high-risk anatomical characteristics, including PFO size, atrial septal hypermobility, and atrial septal aneurysm.[16]

However, it is unclear to what extent elderly patients derive benefits from PFO closure, given that small retrospective studies have not provided definitive answers that are similar to DEFENSE-PFO, because they limited the duration of follow-up and the number of enrolled patients older than 55 years, with even fewer over 65 years of age. For example, a single-center retrospective cohort study identified 14 elderly patients (mean age of 75.2 years) with high-risk PFO and prior cerebrovascular event who underwent PFO closure; after 2.6 ± 1.8 years of follow-up, none of them had recurrent cerebrovascular events, and complications were not greater than expected.[17] Although this was a positive result in this very advanced age group, the small sample size and short duration of follow-up stand out as limitations. Another contemporary series with a longer mean follow-up period (4.5 years) included 458 patients who underwent PFO closure for cryptogenic

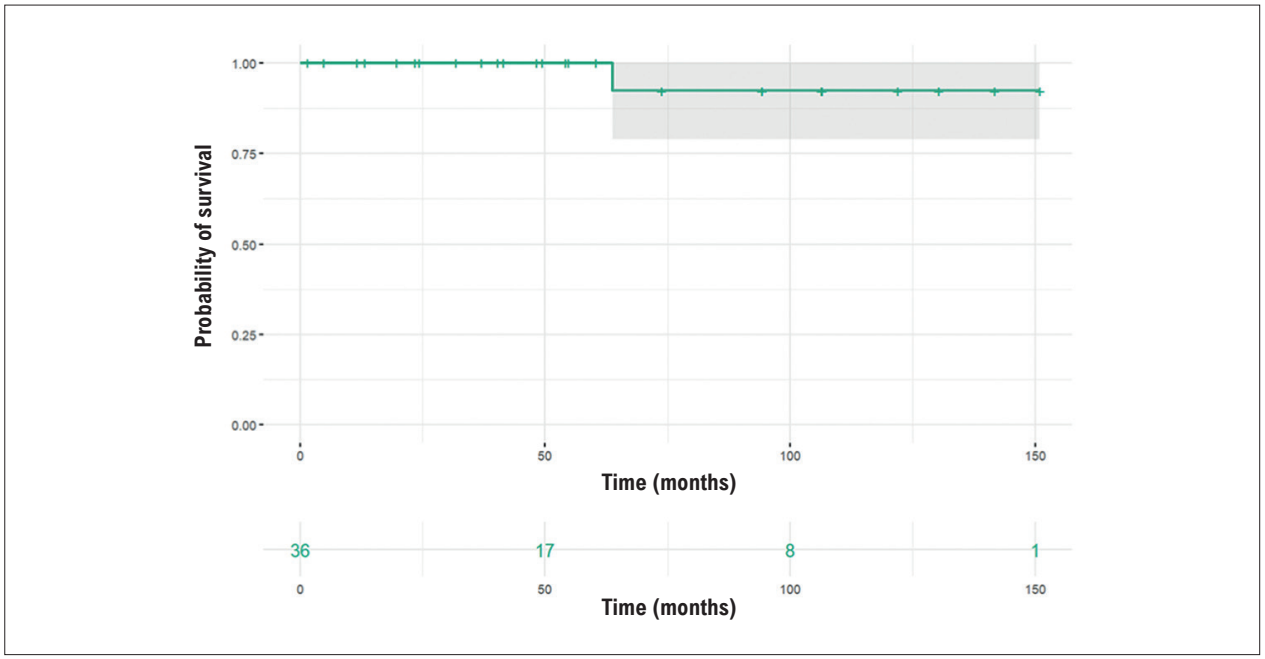

Figure 1 – *Kaplan-Meier curve. The line below the curve shows patients at risk of events over time*

cerebral ischemia,[18] and the 151 patients over 55 years of age had a higher risk of recurrent ischemia, age being the only independent predictor; the majority of events occurred more than 3 years after the procedure and, therefore, were not associated with periprocedural complications. Neither group presented significant residual shunt, which would explain the increase in recurrent events due to mechanisms unrelated to PFO. Accordingly, the authors concluded that recurrent events were likely associated with underlying conditions in the elderly population.

The challenge in this age group lies in selecting patients with high-risk anatomy and a likelihood of the neurological event being related to the PFO.[19] In our study, all patients had ischemic stroke unrelated to important atherosclerotic burden or diagnosed atrial fibrillation; 25% of them, in addition to ischemic stroke, had transient ischemic attacks, and 13.8% had multiple cerebral infarctions.

Under these conditions, it was important to evaluate the anatomical characteristics of the foramen ovale that pose a risk. Among them, the most common is the interatrial septal aneurysm, characterized by increased mobility of part or all of the atrial septum, which can project into either atrium,[10,20,21] with a prevalence of 2.2% to 4%,[22,23] according to transesophageal echocardiography studies. When examined in patients with stroke, the prevalence of atrial septal aneurysm increases significantly. In a study using transesophageal echocardiography, 7.9% of patients with stroke were diagnosed with atrial septal aneurysm.[22] All patients selected for our study had interatrial septal aneurysm.

The Eustachian valve, a remnant of the embryonic right valve of the sinus venosus, is another relevant structure, present in 25% of our patients, and it is more frequently observed in patients with suspected paradoxical embolism compared to control patients.[24] The increased RoPE associated with the presence of the Eustachian valve in patients with PFO can be explained by the valve's ability to direct blood flow from the inferior vena cava towards the fossa ovalis.

The Chiari network is another anatomical risk characteristic, found in 8.3% of our sample. It is a remnant of the right sinus venosus valve whose role is not yet fully understood,[18] originating in a region of the Eustachian and Thebesian valves and attaching to the upper wall of the right atrium or the atrial septum, with a prevalence of 2% to 3%, according to autopsy studies.[25] A frequent association has been found between Chiari networks and PFO, with 83% of patients presenting both. Significantly large right-to-left atrial shunts have been more frequently found in patients with Chiari networks than in controls (55% versus 12%, $p < 0.001$), and this study also reported an association between Chiari networks and interatrial septal aneurysm in 24% of patients. Furthermore, Chiari networks are more common in patients with ischemic stroke compared with those evaluated for other indications (4.6% versus 0.5%), and they may facilitate paradoxical embolism.[26]

The magnitude of the right-to-left interatrial shunt is the quantification of the physiological severity of the foramen ovale, seeing that spontaneous shunt was found in 38.9% of our patients, while the other 61.1% had a large shunt with Valsalva maneuver. A small shunt is considered when there are 3 to 10 bubbles; a medium shunt is considered when there are 10 to 30 bubbles, and a large shunt is considered when there are more than 30 bubbles counted in the first 6 beats after injection.[27]

The RoPE score is an attempt to assign a probability of causal relationship to individual PFOs in the context of ischemic stroke of unknown cause, which may be useful in helping to guide decisions. However, it should always be used in conjunction with other parameters, because the quality of evidence from internal validation studies is, at best, moderate. Furthermore, the RoPE score does not take into account high-risk PFO anatomical features (for example, interatrial septal aneurysm), which have been shown to correlate with greater RoPE. For this reason, we used the prospectively validated PASCAL risk stratification system.[9] As illustrated in Chart 1, patients can be classified into 3 subgroups based on the following 2 domains: (1) high-risk PFO characteristics defined as the presence of a large shunt (> 20 bubbles), interatrial septal aneurysm, or both; and (2) RoPE score, dichotomized as 7 to 10 versus 0 to 6. The RoPE score includes age, history of hypertension, diabetes, smoking, remote history of stroke or TIA, and cortical infarction on imaging. Higher RoPE scores indicate a greater attributable risk of ischemic stroke. Patients are classified as "probable" if they have a high-risk PFO and RoPE score ≥ 7, and they have a 90% relative reduction in recurrent ischemic stroke with closure. Thus, patients are classified as "possible" in the following 2 scenarios: (1) high-risk PFO and RoPE score < 7 or (2) low-risk PFO (absence of large shunt and interatrial septal aneurysm) and RoPE score ≥ 7, showing a 62% relative reduction in recurrent ischemic stroke with closure. Patients are classified as "unlikely" if they have a low-risk PFO and RoPE score < 7. There is no significant difference between percutaneous occlusion versus medical therapy among patients in the "unlikely" category.[9] All patients enrolled in our study had a PASCAL classification of "probable."

Chart 1 – Risk of recurrent stroke in patients with PFO according to PASCAL

		High-risk PFO (ASA, large shunt)	
		No	Yes
RoPE Score	< 7	Unlikely	Possible
	≥ 7	Possible	Probable
		Recurrent stroke prevention	Late AF
Events among 1000 patients over 2 years	Unlikely	–2	18
	Possible	21	3
	Probable	21	6

AF: atrial fibrillation; ASA: atrial septal aneurysm; PASCAL: PFO-Associated Stroke Causal Likelihood risk stratification system; PFO: patent foramen ovale; RoPE: Risk of Paradoxical Embolism. Adapted from Sposato et al.[40]

When addressing the causes of embolic ischemic stroke in elderly patients, it is fundamental to mention atrial fibrillation, which was excluded in our patients by means of 24-hour Holter monitoring, assessment of left atrial volume, presence of thrombus in the left atrial appendage, and its emptying rate. Its undetected or hidden presence is associated with a 2.5-fold increase in the risk of stroke, although with limited temporal impact.[28]

Some studies have also examined the relationship between atrial tachyarrhythmias detected by implantable devices and the risk of thromboembolic events.[29,30] These studies have shown that high atrial heart rates were associated with an increased risk of developing atrial fibrillation and events such as ischemic stroke. The presence of prolonged episodes of high atrial rate was related to a higher risk of ischemic stroke and systemic embolism, comparable to the risk presented by individuals with clinically diagnosed atrial fibrillation. Although the relationship between tachyarrhythmias and embolic events is evident, the cause and timing need to be better understood, given that not all patients with thromboembolic events had tachyarrhythmias detected in the preceding days.

This scenario suggests that atrial fibrillation may be a risk marker for thromboembolic events, but its direct link with these events may be more complex than previously thought.[29] It is also important to mention that PFO closure is associated with a 5-fold higher risk of atrial fibrillation compared with medical treatment.[30] In our series, only 1 patient developed atrial fibrillation 1 year after the procedure; therefore, it was not related to the prosthesis. Data from clinical trials indicate that up to 6.6% of patients with ischemic stroke who undergo PFO closure develop atrial fibrillation in the following weeks, with 83% of cases being detected within 45 days after the procedure. The risk of atrial fibrillation after PFO closure is usually transient, with 59% of cases resolving within 2 weeks of onset,[14] and incidence increases with age.[31,32] For example, in a cohort of 1,221 patients with ischemic stroke who underwent PFO closure, the incidence of new atrial fibrillation among patients over 60 years of age was 2.66 per 100 patient-years, compared to 0.49 per 100 patient-years in those under 60 years.[32] Furthermore, in the same manner as other patients with ischemic stroke, the diagnosis of atrial fibrillation after PFO closure increases with the duration of cardiac monitoring.[33]

A study of 225 patients undergoing PFO closure who were monitored with loop recorders for 28 days after the procedure revealed that 47 (20.9%) had supraventricular tachycardia lasting more than 30 seconds. In this study, age, male sex, and a device with a disk > 25 mm were independently associated with an increased risk of supraventricular arrhythmias.[33] In another single-center, retrospective, observational study, 35 of 761 patients who underwent PFO closure were monitored for a mean of 12 months (54.6 weeks) with implantable loop recorders.[34] Of these, 13 patients (37%) developed atrial fibrillation during follow-up. The majority of cases were diagnosed within the first 4 weeks of monitoring, and they resolved within 3 months, without recurring during follow-up.

Accordingly, it is important to investigate the role of prolonged cardiac monitoring after PFO closure and the clinical implications of atrial fibrillation occurrence in the risk of recurrent ischemic stroke.

Furthermore, a variety of medical treatments have been used, based on data from secondary prevention studies on ischemic stroke in general and studies on cryptogenic stroke in particular; however, there are no published randomized controlled trials that have evaluated the efficacy of individual medications specifically in strokes associated with PFO.

The basis for exclusively medical treatment of patients with PFO also lacks robust scientific evidence, considering that the trials were almost exclusively observational, with only one randomized controlled trial comparing oral anticoagulants and antiplatelet agents. A meta-analysis of randomized controlled trials showed a recurrent stroke rate of 1.27 events per 100 patient-years with medication alone,[35] whereas, in another meta-analysis of randomized controlled trials, the incidence of recurrent stroke with medical therapy was 4.6%, with a mean follow-up of 3.8 years.[36]

Despite severe heterogeneity of results, the most recent meta-analysis is consistent in the view that antiplatelet agents are useful in preventing stroke. Although the overall quality of the evidence is very low, the superiority of oral anticoagulants versus antiplatelet agents was also evident when only studies with multivariate adjustment were considered.

Safety reports have often been incomplete or have produced inconsistent results. In a meta-analysis of observational studies, 1.1% of patients receiving medical therapy experienced bleeding complications.[36] This surprisingly low proportion of bleeding episodes may be explained by the young age of the patients and the short follow-up, and it should be interpreted with caution because the majority of these patients will undergo lifelong medical therapy with an incremental risk of bleeding with aging. In patients with PFO, an odds ratio of 4.57 was found for major bleeding with oral anticoagulants versus antiplatelet medications. A previous meta-analysis that considered secondary prevention of stroke in general revealed that the potential benefit of oral anticoagulants may be outweighed by the risk of intracranial hemorrhage (odds ratio 2.54) and severe extracranial hemorrhage (odds ratio 3.43).[37]

It is worth emphasizing that elderly patients represent a higher risk of hemorrhagic complications than the general population. In our sample, 75% of patients had a HAS-BLED[12] score of 2 or 3, meaning a bleeding risk of 1.88% to 3.74% per year (Table 1). Although the HAS-BLED score was not designed for this purpose, it can help identify the population at risk of bleeding events. The use of anticoagulants before the procedure was 41.6%, falling to 5.6% after PFO occlusion, a reduction of 86.6% ($p = 0.03$), implying a lower exposure to hemorrhagic complications in these patients. The high number of patients using anticoagulation before the procedure is noteworthy in our series. Perhaps the lack of clinical trials in patients in this age group, with previous ischemic stroke, PFO with high-risk anatomy, and concerns regarding hidden atrial fibrillation have led physicians to be more aggressive in prevention, but more data are needed to elucidate these findings. Moreover, in patients who need to use oral anticoagulants, non-coumarin anticoagulants may alter the risk-benefit ratio,[38,39] but there are no data in the literature related to these patients.

Although randomized clinical trials in elderly patients with PFO are limited, it is believed that occlusion is indicated in cases of risk anatomy and history of ischemic stroke, following

the same treatment logic applied to younger patients. The fact that a patient is over the age of 60 does not rule out the chance of an ischemic stroke being related to the foramen ovale. It is essential to carefully consider the risk of the procedure, life expectancy, and exclusion of other possible causes of ischemic cerebrovascular events in this age group.

Study limitations

Our study has important limitations, the main ones being the small number of patients and the fact that it was a retrospective study from a single center, with a team experienced in these procedures. Moreover, atrial fibrillation was not completely ruled out as a cause of ischemic stroke; we took into account the history, 24-hour Holter monitoring, and left atrial characteristics, but no patient used an event monitor for 6 months. Its occurrence after the procedure may also be underestimated, since only clinical criteria were applied, without electrocardiographic monitoring in the first 30 days. Longer clinical follow-up could also better stratify the risk of recurrence of ischemic neurological events in these patients and the impact on the reduction of bleeding events with less use of anticoagulation after PFO occlusion.

Conclusion

Percutaneous PFO occlusion for the prevention of cerebrovascular events in individuals over 60 years of age with prior stroke is effective, with a low risk of complications, including the risk of post-procedure atrial fibrillation. We can also reduce the chance of bleeding in these patients by reducing the use of anticoagulants after PFO occlusion. However, it is not possible to generalize all these results, considering that this was an observational study, with the limitations highlighted in the text. It is fundamental to correctly select patients with high-risk anatomy and to rule out the most common causes of ischemic stroke in this age group.

Author Contributions

Conception and design of the research and statistical analysis: Sabedotti M, Selistre LS; acquisition of data: Sabedotti M, Mezzomo A, Voltolini S, Maggi B; analysis and interpretation of the data: Sabedotti M, Selistre LS, Camazzola FE, Degrazia RC; writing of the manuscript: Sabedotti M, Mezzomo A, Maggi B; critical revision of the manuscript for intellectual content: Sabedotti M, Selistre LS, Camazzola FE, Mezzomo A, Degrazia RC, Voltolini S, Maggi B

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Study Association

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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee on Animal Experiments of the Universidade de Caxias do Sul under the protocol number 79548824.5.0000.5341.

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