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Five Year Follow-Up of Cryptogenic Stroke Patients Following Pfo Closure

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Abstract: *Background and Objectives*: According to guidelines PFO closure is recommended for secondary stroke prevention in patients with cryptogenic stroke [1]. Paradoxial embolism from PFO mediated right to left shunt has been described as the mechanism of stroke in these cases [2]. The aim of the study is to follow-up patients after PFO closure and determine the long-term effectiveness on reccurent stroke risk reduction. *Materials and Methods*: A total of 103 patients were enrolled in a retrospective study and followed-up by phone up to five years after PFO closure. Standardized survey was conducted about their well-being, recurrent cerebrovascular events, and the use of prescribed medication. Patients were also followed up for residual shunts 24 h, 30 days, 1 and 2 years after PFO. The pathogenic ischemic stroke subtypes are determined using CCS (Causative Classification System for Ischemic Stroke). *Results*: 43.7% (n = 45) of patients were male. The mean age – 44.4 ± 13 (18–75). 53.4% (n = 55) of patients with possible cardio-aortic embolism the most probable cause for cryptogenic stroke was PFO. Residual shunts were mostly observed in patients with Amplatzer occluder – 87.5% (n = 14). There was correlation between residual shunt and increased risk of transient ischemic attack recurrence (p = 0.067). Five-years after PFO closure recurrent cerebrovascular events were reported in only 5.1% (n = 5) of patients, this difference is statistically relevant (p < 0.001). Out of 51 patient presented with complaints before PFO closure, 25.5% (n = 13) did not present with any complaints after PFO closure. *Conclusions*: PFO can be considered a possible risk factor for cryptogenic stroke. PFO closure is effective in reducing recurrent cerebrovascular events. Residual shunt after PFO closure increases the risk of transient ischemic attack recurrence. Amplatzer occluder device is associated with a higher risk for residual shunts after PFO closure. PFO closure can be associated with improvement of complaints.

Keywords: patent foramen ovale; patent foramen ovale closure; cryptogenic stroke; paradoxical embolism; recurrent stroke; secondary stroke prevention

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1. Introduction

Patent Foramen Ovale (PFO) is a normal fetal communication between the right and left atria that closes soon after birth. In 20–34% of the population PFO persists [3]. Usually it is asymptomatic, but is has been associated with decompression illness, systemic arterial embolism, obstructive sleep apnea, and migraine with aura [4]. In some cases, PFO can cause a paradoxical embolism mediated from an interatrial shunt, that has been described as the mechanism of cryptogenic stroke, particularly in young adults, therefore,

prevention of recurrence is of paramount importance. A cryptogenic stroke is generally defined as a stroke of unknown cause that is now thought to comprise about 25% of all ischemic strokes [2]. The therapeutic possibilities for PFO range from conservative treatment (antithrombotic treatment) to its percutaneous closure using various types of occluders [5]. According to the latest guidelines of American Academy of Neurology (AAN) (2017) in patients younger than 60 years with a PFO and embolic-appearing infarction and no other mechanism of stroke identified, clinicians may recommend closure following a discussion of potential benefits and risks (level C). In patients who opt to receive medical therapy alone without PFO closure, clinicians may recommend an antiplatelet medication such as aspirin or anticoagulation (level C) [1]. Data from 6 major trials (CLOSURE I, PC Trial, RESPECT, CLOSE, REDUCE, and DEFENSE-PFO) demonstrates the superiority of PFO closure over medical management alone in preventing cryptogenic stroke recurrence [6,7].

The aim of the study is to follow-up patients after PFO closure and determine its long-term effectiveness on recurrent cerebrovascular event (stroke (CS) or transient ischemic attack (TIA)) risk reduction.

2. Materials and Methods

2.1. Study Design and Patient Population

A single-center (Pauls Stradiņš Clinical University Hospital) prospective – retrospective study was performed on patients who underwent a PFO closure procedure between years 2004 and 2019.

2.2. Evaluations

Transthoracic echocardiogram (TTE) was performed and evaluated by cardiologists.

Ischemic stroke diagnosis was made by neurologists. The pathogenic subtypes of ischemic stroke were determined using CCS (Causative Classification System for Ischemic Stroke) [8] by a radiologist.

2.3. Baseline Study Assessment

At first, a list was obtained from hospitals digital database of patients who underwent PFO closure procedure at Pauls Stradiņš Clinical University Hospital between years 2004 and 2019. Inclusion criteria for study participants:

- Subjects at least 18 years of age.
- Subjects who have been diagnosed with Patent Foramen Ovale (PFO).
- Subjects who have undergone PFO closure procedure at Pauls Stradiņš Clinical University Hospital between years 2004 and 2019.

Afterwards data from hospitals digital database about each patient was collected – personal information (personal code, phone number), what kind of radiological exams were done during hospitalization (CT, CTA, MR, MRA, TTE, Doppler ultrasound) and their findings, type of the atrial septal defect (ostium secundum, ostium primum, sinus venosus, PFO, post-operative iatrogenic defect), date of PFO closure, at what age PFO closure was done, PFO occluder type (amplatzer, cardia, cardia ultra, helex), PFO occluder size, implantation (percutaneous, transcatheter), surgeon performing PFO closure procedure, days of hospitalization, intrahospital complications, associated anomalies (abnormal pulmonary vein drainage, mitral valve prolapse, PDA, VSD), was there an atrial septal aneurysm, are there any arrhythmias in patients history (atrial fibrillation, atrial flutter, supraventricular tachycardia, arteriovenous blockage, sinus node dysfunction), atrial fibrillation type (permanent, persistent, paroxysmal), previous cerebrovascular events – what kind (ischemic stroke, transient ischemic attack) and how many, heart failure (class 1–4), previous myocardial infarctions, previously done percutaneous coronary intervention (PCI), does patient have hypertension and/or diabetes.

When all previously listed information about the patient was collected, pathogenic subtype of ischemic stroke was determined using CCS and patients were followed-up by

phone 30 days, 3 and 6 months, 1, 2, 3, 4 and 5 years after PFO closure. During the first call (day 30 after PFO closure) standardized survey was conducted – does the patient have any symptoms after stroke (impaired memory, coordination, speech, vision, paresis, headaches), did the patient have any other complaints before PFO closure (headaches, fatigue, dizziness, visual impairment, palpitations), to what floor can they climb to (cardiac stress test), what kind of medication do they use, comorbidities, bad habits (smoking, alcohol), lifestyle (sitting, physical), height and weight (so that BMI can be calculated). Each time the patient was also called and questioned about recurring cerebrovascular events (ischemic stroke or transient ischemic attack), complaints after PFO closure (headaches, fatigue, dizziness, visual impairment, palpitations) and complications after PFO closure (arrhythmias, shunt).

Patients were also followed up for residual shunts 24 h, 30 days, 1 and 2 years after PFO closure by a cardiologist using ECHO-KG.

2.4. Statistical Analysis

All previously listed results were summarized using "Microsoft Excel" and analyzed using "IBM SPSS" software. The mean, range, and standard deviation were calculated for quantitative data. Before and after results were compared using the McNemar's test. Pearson's Chi-square, Fisher tests, were used to analyze qualitative data. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. *Baseline Characteristics of Study Participants*

A total of 103 patients were enrolled in the study. Baseline characteristics of study participants are presented in Table 1.

Overall, 91 patients were younger than 60 years, 12 patients were 60 years and older – youngest patient being 18 and oldest patient being 75 years of age.

The prevalence of interatrial septal aneurysms was 16.5%.

Table 1. Baseline characteristics of study participants.

Sex	Men, % (n)	43.7 (n = 45)
	Women, % (n)	56.3 (n = 58)
Mean age, years (SD)		44.4 (SD 13)
Mean body mass index, kg/m^2 (SD)		26.7 (SD 5.3)
Smokers, % (n)		32 (n = 33)
Sedentary lifestyle, % (n)		68 (n = 70)
Associated heart anomalies – ventral septal defect (VSD), % (n)		1 (n = 1)
Atrial septal aneurysm (ASA), % (n)		16.5 (n = 17)
Atrial fibrillation (AF), % (n)		5.8 (n = 6)
Type of atrial fibrillation	Paroxysmal, % (n)	4.9 (n = 5)
	Persistent, % (n)	1 (n = 1)
Myocardial infarction, % (n)		1.9 (n = 2)
Percutaneous coronary intervention, % (n)		1.9 (n = 2)
Arterial hypertension (AH), % (n)		35.9 (n = 37)
Chronic heart failure, % (n)		14.6 (n = 15)
NYHA Functional Heart failure Classification	I class, % (n)	7.8 (n = 8)
	II class, % (n)	6.8 (n = 7)
Mean exercise tolerance, to what floor can the patient climb (SD)		3.9 (SD 1.2)
Diabetes, % (n)		3.9 (n = 4)

Atherosclerosis, % (*n*)	3.9 (*n* = 4)
Dyslipidemia, % (*n*)	33 (*n* = 34)
Hypercholesterinemia, % (*n*)	10.7 (*n* = 11)
Migraine, % (*n*)	4.8 (*n* = 5)

Quantitative normally distributed data (Kolmogorov-Smirnov test) are presented as mean (standard deviation (SD)), categorical nominal values are presented with %, frequencies (*n*, number of patients).

3.2. Cerebrovascular Event Characteristics before PFO Closure

92.2% (*n* = 95) of patients had at least 1 cerebrovascular event before PFO closure. Most common event was CI – 84.5% (*n* = 87), less common was TIA – 14.6% (*n* = 15). 7.4% (*n* = 7) of patients have had both CI and TIA before PFO closure. 16.5% of patients had 1 cerebrovascular event before PFO closure, 14.6%–2 events. The biggest number of events was 5, which was seen in 1.9% of patients. In 5-year time, only 1 patient with ASA had recurrent TIA and no patients with ASA had recurrent CI. Cerebrovascular event characteristics before PFO closure are presented in Table 2.

Table 2. Cerebrovascular event characteristics before PFO closure.

Previous cerebrovascular events, % (*n*)		92.2 (*n* = 95)
Previous cerebrovascular events	Ischemic stroke, % (*n*)	84.5 (*n* = 87)
	Transient ischemic attack, % (*n*)	14.6 (*n* = 15)
	Both, % (*n*)	7.4 (*n* = 7)
Number of cerebrovascular events	0, % (*n*)	7.8 (*n* = 8)
	1, % (*n*)	16.5 (*n* = 69)
	2, % (*n*)	14.6 (*n* = 17)
	3, % (*n*)	5.8 (*n* = 6)
	4, % (*n*)	1 (*n* = 1)
	5, % (*n*)	1.9 (*n* = 2)

Categorical nominal values are presented with %, frequencies (*n*, number of patients).

According to CCS for 66.7% (*n*=58) of patients the pathogenic subtype of CI was possible cardio-aortic embolism and for 1.1% (*n* = 1) - evident cardio-aortic embolism. Patients with arterial fibrillation were excluded as that has been identified as the cause of cryptogenic stroke. Therefore 4 patients in total were excluded. For 53.4% (*n* = 55) of patients with possible cardio-aortic embolism the most probable cause for cryptogenic stroke was PFO. Pathogenic subtypes of CI are presented in Table 3.

Table 3. Pathogenic subtypes of CI.

Possible cardio-aortic embolism, % (*n*)	66.7 (*n* = 58)
Evident small artery occlusion, % (*n*)	19.5 (*n* = 17)
Evident supra-aortic large artery atherosclerosis, % (*n*)	8 (*n* = 7)
Unclassified, % (*n*)	2.3 (*n* = 2)
Probable supra-aortic large artery atherosclerosis, % (*n*)	1.1 (*n* = 1)

Categorical nominal values are presented with %, frequencies (*n*, number of patients).

3.3. PFO Closure Procedure Characteristics

CT scan was done in 54.7% (*n* = 52) of patients who have had a cerebrovascular event. CTA in 47.4% (*n* = 45) of patients, MR – 45,3% (*n* = 43) and MRA – 21,1% (*n* = 20).

The mean age for patients undergoing PFO closure procedure was 44.4 years (SD 13). For 3.9% (*n* = 4) of patients the PFO closure was unsuccessful - these patients were excluded from the statistics moving forward. Therefore, the procedures success rate is 96.1%. All patients underwent percutaneous device implantation. The most common type

of implantation device (occluder) used was Amplatzer – 58.6% (*n* = 58), less frequently used were Cardia Ultrasept device – 39.4% (*n* = 39). Mean septal occluder size was 24.8 (SD 4.2) mm, of which the smallest was 10 mm and the largest 35 mm. Most used occluder size was 25 mm – 78.8% (*n* = 78). The average hospital stay was 2.2 (SD 0.5) days, minimum being 2 days and maximum – 4 days. Residual shunt 24 hours post-op was observed in 9.1% of patients, and no patients had intrahospital complications. Residual shunts were mostly observed in patients with Amplatzer occluder – 87.5% (*n* = 14), for patients with Cardia Ultrasept occluder residual shunts were observed in only 1% of patients. PFO closure procedure characteristics are presented in Table 4.

Table 4. PFO closure procedure characteristics.

Mean age at the time of procedure, years (SD)		44.4 (SD 13)
Unsuccessful PFO procedure, % (*n*)		3.9 (*n* = 4)
Type of implantation	Percutaneous, % (*n*)	100 (*n* = 99)
Implantation device	Amplatzer, % (*n*)	58.6 (*n* = 58)
	Cardia, % (*n*)	21.2 (*n* = 21)
	Cardia Ultra, % (*n*)	18.2 (*n* = 18)
	Helex, % (*n*)	2 (*n* = 2)
Mean size of the implanted device, mm (SD)		24.8 (SD 4.2)
Mean hospital stay, days (SD)		2.2 (SD 0.5)
Residual shunt 24 hours post-op, % (*n*)		9.1 (*n* = 9)
Intrahospital complications, % (*n*)		0 (*n* = 0)

Quantitative normally distributed data (Kolmogorov-Smirnov test) are presented as mean (standard deviation (SD)), categorical nominal values are presented with %, frequencies (*n*, number of patients).

3.4. Cerebrovascular Event Characteristics after PFO Closure

All patients used antithrombotic therapy for 6 months after PFO closure procedure. Secondary stroke prevention with antiplatelet agents (aspirin) after six months is still being used in 55,6% (*n*=55) of patients, oral anticoagulants (dabigatran, rivaroxaban) – 6,1% (*n*=6). 59,6% (*n*=59) of patients stopped using antithrombotic therapy after the first 6 month.

After PFO closure patients were followed for up to 5 years. Residual shunts after 30 days were observed in 2% (*n* = 2) of patients (from 99 patients included), after 1 year in 7.1% (*n* = 7) (from 99 patients included), and after 2 years in 2.3% (*n* = 2) (from 86 patients included). In total 16.2% (n = 16) had residual shunt after PFO closure.

TIA in 5-year time after PFO closure was observed in only 3% (*n* = 3) of patients. 1% (*n* = 1) of patients had it 1 year after PFO closure (from 99 patients included), 1.2% (*n* = 1) 2 years after (from 86 patients included) and 1.8% (*n* = 1) 4 years after PFO closure. 1 patient had a recurrent TIA after PFO closure and 2 patients had TIA after PFO closure, without having had any before, this difference is not statistically relevant (*p*=0.393).

CI in 5-year time after PFO closure was observed in only 3% (*n* = 3) of patients. 2% (*n* = 2) of patients had it 6 months after PFO closure (from 99 patients included) and 1.4 % (*n* = 1) 3 year after (from 69 patients included). No patients who did not have CI before PFO closure had CI after, however 3 patients had recurrent CI after PFO closure, this difference is not statistically relevant (*p* = 0.586). Before PFO closure 92,2% (*n* = 95) of patients had at least one cerebrovascular event and in five-year time after PFO closure recurrent cerebrovascular events were reported in only 5,1% (*n* = 5) of patients, this difference is statistically relevant ($p < 0.001$).

There was no correlation between residual shunt after PFO closure and increased risk of stroke recurrence in 2 years' time – none of 16 patients who had residual shunt after PFO closure, had recurrent stroke, this difference is not statistically relevant (*p* = 0.596).

However, there was correlation between residual shunt after PFO closure and increased risk of TIA recurrence in 2 years' time – from 16 patients who had residual shunt after PFO closure 2 had recurrent TIA, this difference is statistically relevant ($p = 0.067$).

3.5. Patient Complaints

51.5% ($n = 51$) of patients had complaints before PFO closure (headaches, fatigue, dizziness, visual impairment, heart palpitations) – some of these complaints were associated with previous CI, but majority of them were independent. 38.4% ($n = 38$) of patients complained of headaches (including migraines and chronic headaches), 6.1% (n=6) complained of fatigue, 18.2% ($n = 18$) complained of dizziness, 7.1% ($n = 7$) of visual impairment and 7.1% ($n = 7$) of heart palpitations.

4% ($n = 4$) of patients after 30 days experienced heart palpitations (from 99 patients included), after 1 year – 6.1% ($n = 6$) (from 99 patients included) and after 2 years – 2.3% ($n = 2$) (from 86 patients included). 7 patients complained of heart palpitations after PFO closure although they did not have these complaints before, and only for 1 of 7 patient's complaints of heart palpitation persisted after PFO closure, this difference is not statistically relevant ($p = 0.390$)

1% ($n = 1$) of patients after 30 days experienced fatigue (from 99 patients included), after 3 months – 1% ($n = 1$) (from 99 patients included) and after 3 years – 1% ($n = 1$) (from 69 patients included). There were no new complaints of heart palpitations observed after PFO closure, and only for 2 of 7 patients complaints persisted after PFO closure, this difference is statistically relevant ($p = 0.003$).

6.1% ($n = 6$) of patients after 30 days experienced dizziness (from 99 patients included), after 3 months – 7.1% (n = 7) (from 99 patients included), after 6 months – 8.1% ($n = 8$) (from 99 patients included), after 1 year – 8.1% (n = 8) (from 99 patients included), after 2 years – 8.1% ($n = 7$) (from 86 patients included), after 3 years – 4.3% ($n = 3$) (from 69 patients included), after 4 years – 5.4% (n = 3) (from 56 patients included) and after 5 years – 4.7% ($n = 2$) (from 43 patients included). For half of the patients ($n = 9$) complaints of dizziness persisted after PFO closure, and for 5 people dizziness was a new complaint after PFO closure, this difference is statistically relevant ($p<0.001$).

2% ($n = 2$) of patients after 30 days experienced visual impairment (from 99 patients included), after 3 months – 3% ($n = 3$) (from 99 patients included), after 6 months – 3% (n = 3) (from 99 patients included), after 1 year – 3% ($n = 3$) (from 99 patients included), after 2 years – 2.3% ($n = 2$) (from 86 patients included), after 3 years – 1.4% ($n = 1$) (from 69 patients included) and after 4 years – 1.8% ($n = 1$) (from 56 patients included). There were no new complaints of visual impairment after PFO closure, however for 4 patients complaints persisted after PFO closure, this difference is statistically relevant ($p < 0.001$).

13.1% ($n = 13$) of patients after 30 days experienced headaches (from 99 patients included), after 3 months – 15.2% ($n = 15$) (from 99 patients included), after 6 months – 17.2% ($n = 17$) (from 99 patients included), after 1 year – 17.2% ($n = 17$) (from 99 patients included), after 2 years – 18.6 % ($n = 16$) (from 86 patients included), after 3 years – 13% (n = 9) (from 69 patients included), after 4 years – 17.9% ($n = 10$) (from 56 patients included) and after 5 years – 18.6% ($n = 8$) (from 43 patients included). There were 2 patients with new complaints of headaches after PFO closure, and for only half of the patients ($n = 19$) complaints of headaches persisted after PFO closure procedure, this difference is statistically relevant ($p < 0.001$).

Out of 51 patients presented with complaints before PFO closure (headaches, fatigue, heart palpitations, dizziness, visual impairment), 25.5% ($n = 13$) did not present with any complaints after PFO closure, this difference is statistically relevant ($p = 0.017$). All patients with headaches and migraines noted that after PFO closure the symptoms were much less frequent and painful.

4. Discussion

Despite this study being with a small number of patients, it demonstrates that PFO percutaneous closure with occluders is safe and effective, with the success rate of 96.1%. From 99 patients included in this study, there were no deaths and no intrahospital complications.

The most used implantation device was Amplatzer occluder (58.6%), the Amplatzer occlude and Gore Cardioform Septal Occluder (not used in our research) are the only devices that has FDA approval for PFO closure in the context of cryptogenic stroke [9]. Residual shunt after PFO closure was observed in 16.2% (n = 16) of patients. In comparison with literature, residual shunts may be observed in up to 25%, with unclear clinical significance [10]. 87,5% of residual shunts were observed directly with the Amplatzer occluder, however for patients with Cardia Ultrasept occluder residual shunts were observed in 1% of patients. Therefore, Cardia Ultrasept occluder could be considered more efficient than Amplatzer occluder. Some research do suggest that the presence of residual shunt are associated with an increased risk for stroke or TIA recurrence [11]. In our research there was no correlation between residual shunt and increased risk of stroke recurrence, however, there was a correlation between residual shunt and increased risk of TIA recurrence (p = 0.067).

The prevalence of interatrial septal aneurysms (ASA) was 16.5%. For patients with PFO-associated stroke, ASA is an important predictor of recurrent stroke [12]. In 5-year time, only 1 patient with ASA had recurrent TIA.

According to CCS for 66.7% (n = 58) of patients the pathogenic subtype of CI was possible cardio-aortic embolism and for 1.1% (n = 1) - evident cardio-aortic embolism. Patients with arterial fibrillation should be excluded as that has been an identified as the cause of cryptogenic stroke. Therefore, the 1 patient with evident cardio-aortic embolism, and 3 patients with possible cardio-aortic embolism were excluded. For 53.4% (n = 55) of patients with possible cardio-aortic embolism the most possible cause for cryptogenic stroke is PFO.

Before PFO closure 92,2% (n = 95) of patients had at least one cerebrovascular event and in five-year time after PFO closure recurrent cerebrovascular events were reported in only 5.1% (n = 5) of patients (p < 0.001). This clearly shows that PFO closure procedure is effective in reducing recurrent cerebrovascular events.

Out of 51 patients presented with complaints before PFO closure (headaches, fatigue, heart palpitations, dizziness, visual impairment), 25.5% (n = 13) did not present with any complaints after PFO closure, this difference is statistically relevant (p = 0.017). There are many contributing factors that could play a role in patient's complaints; therefore, it is hard to say whether these changes are only because of PFO closure, however it can be assumed that PFO closure can be associated with improvement of complaints. A lot of patients with headaches and migraines noted that after PFO closure the symptoms were much less frequent and less painful.

5. Conclusions

- PFO can be considered a possible risk factor for cryptogenic stroke.
- PFO closure is effective in reducing recurrent cerebrovascular events.
- Residual shunt after PFO closure increases the risk of transient ischemic attack recurrence.
- Amplatzer occluder device is associated with a higher risk for residual shunts after PFO closure.
- PFO closure can be associated with improvement of complaints (headaches, fatigue, heart palpitations, dizziness, visual impairment).

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