Patent foramen ovale: to close or not to close – still the question

Drożny otwór owalny: zamykać czy nie zamykać – pytanie wciąż otwarte

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Introduction

Patent foramen ovale (PFO) is a physiological remnant of the foramen ovale, a connection between atria which is essential in fetal circulation. It is assumed to be a normal variant, as it is present in 20-27% of the population in autopsy studies but only in 10-15% of patients in contrast transesophageal echocardiography (TEE) [1]. This discrepancy may be due to increase in size of PFO with age. Patent foramen ovale is a flap-like tunnel between atrial septa: primum and secundum in the location of the fossa ovalis. It is potential communication for right-to-left shunt. Patent foramen ovale usually opens during Valsalva manoeuvre and other physiological situations when pressure in the right atrium exceeds the left atrium, that is when negative pressure in the chest (e.g. during deep breath, cough, sneezing) raises systemic venous return. Patent foramen ovale remains unrecognized and silent in most cases.

The Mayo Clinic autopsy study showed that the size of a PFO increases from a mean of 3.4 mm in the first decade to 5.8 mm in the 10th decade of life, as the valve of the fossa ovalis stretches with age [1]. The prevalence of PFO presence decreasing with age may be due to shorter life of patients with PFO or spontaneous closure. Recent evidence from surgical data show the opposite, that PFO prevalence is not related to age [2].

Patent foramen ovale (PFO) is associated with cryptogenic strokes, recurrent transient neurological deficits, sleep apnoea, decompression illness, and migraines [3].

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A study with diffusion-weighted magnetic resonance imaging brain scanning in patients (n = 60) with non-major acute pulmonary embolism showed that up to 33% (n = 5/15) of the patients with a PFO had silent brain infarcts at admission. This is significantly more common than in patients without a PFO, which was reported at 2% (n = 1/45, p = 0.003) [9]. Numerous retrospective, case-control studies have also shown a higher prevalence of PFO in patients with cryptogenic stroke. The authors of a meta-analysis of these studies reported only a significant association of PFO and atrial septal aneurysm in patients younger than 55 years [10].

On the other hand, there are studies in patients older than 55 years (n = 372), where PFO was significantly more common in cryptogenic stroke patients (28.3%) than in patients with a known cause of stroke (11.9%, p < 0.001) [11]. Similarly, another study, in 132 consecutive patients years after stroke older than 55 years, showed higher prevalence of PFO and atrial septal aneurysm in a subgroup with cryptogenic stroke in comparison with patients with known cause of stroke. It was also true in patients older than 75 years of age [12].

Alsheikh-Ali et al. applied the Bayes theorem to the available data, to ascertain the probability of PFO being incidental in a patient with cryptogenic stroke. They came to the conclusion that PFO may represent an incidental finding in 33-48% of cryptogenic strokes when in isolation, but only in 11% when associated with bulging of the interatrial wall (so-called atrial septal aneurysm – ASA). These figures drop to 20% and 9%, respectively, in patients less than 55 years old [13]. Recently there were several studies published calling into question the link between PFO and stroke.

A cause-effect relationship between PFO and cryptogenic stroke has not been convincingly demonstrated. In particular, the extent of the PFO-related stroke risk in the general population still remains controversial [14]. Furthermore, several studies have consistently found that the presence of a PFO does not inherently increase the risk of recurrent stroke [4, 15-19]. This may be due to the relatively low overall rate of stroke recurrence in patients with cryptogenic stroke and PFO, ranging in studies from 0 to 12% per year, with an average annualized risk across studies of approximately 2% [17, 18]. The higher rate of recurrence in a multicenter, prospective study was observed in patients with both atrial septal aneurysm and PFO, ranging in studies from 0 to 12% per year, with an average annualized risk across studies of approximately 2% [17, 18]. The higher rate of recurrence in a multicenter, prospective study was observed in patients with both atrial septal aneurysm and PFO, ranging in studies from 0 to 12% per year, with an average annualized risk across studies of approximately 2% [17, 18]. The higher rate of recurrence in a multicenter, prospective study was observed in patients with both atrial septal aneurysm and PFO, ranging in studies from 0 to 12% per year, with an average annualized risk across studies of approximately 2% [17, 18].

The occurrence of stroke was not associated with differences in baseline data, the presence of atrial septal aneurysm, PFO size or chosen treatment (PFO closure, anticoagulation, antithrombotic therapy). It should be noted that most patients in this study were treated medically (only 3 had intervention therapy). Also, groups were relatively small. It seems important that patients with subsequent stroke have statistically significantly more multiple risk factors [30]. In another study of 280 patients with mean follow-up of 2.6 years, the recurrence rate was 0.6% per year for patients treated with interventional closure devices and 13% per year for medical treatment with acetylsalicylic acid [31]. The latest study analyses have shown, despite doubts about PFO, that there are in the literature more studies with patients treated with device closure than medically: 7013 patients vs. 1093.

A meta-analysis of observational, non-randomized trials gave conflicting results for one randomized CLOSURE I trial [32, 33]. In the observational studies the incidence rate of recurrent stroke was 0.36 (95% CI 0.24-0.56) events per 100 person-years with closure versus 2.53 (95% CI 1.91-3.35)
events per 100 person-years with medical therapy. The incidence rate for the closure arm in the CLOSURE I trial was higher by almost 4 times (1.34, 95% CI 0.69-2.34) and did not differ from medical treatment. The observational studies are in favour of closing PFO in secondary prevention, but CLOSURE I failed to show superiority of the closing strategy. There are many possible reasons why CLOSURE I failed. First, the lower event rate than previously reported in the medical arm suggests that baseline risk in the trial population was lower. Second, the higher rates in the closure arm may reflect unrealistic estimates in observational studies. Authors are less keen to publish unfavourable results. Third, the researchers failed to select high-risk patients with PFO-related events in the CLOSURE trial. High-risk patients with clinical indicators of paradoxical embolism, such as large shunt, associated atrial septal aneurysm, Valsalva manoeuvre at onset of stroke, evidence of deep vein thrombosis, evidence of a hypercoagulable state, stroke recurrence despite antithrombotic treatment, multiple clinical cerebrovascular events or multiple ischaemic lesions at brain magnetic resonance imaging (MRI) and absence of any conventional stroke risk factor were probably more often treated with closure off-protocol, not included in the trial [13, 34, 35]. Moreover, the 2-year follow-up may be inadequate to fully capture the benefit of the intervention.

Importantly, the number of patients included in observational studies is 10 times larger than the number of patients enrolled in the CLOSURE I trial. In summary, the results of the CLOSURE I challenge the credibility of observational evidence strongly favouring mechanical closure over medical therapy [32].

Although PFO is often closed as secondary prevention in cryptogenic stroke, the benefit of this treatment remains unclear. The RoPE study concerns developing a risk model for application to ongoing randomized trials of percutaneous PFO closure for cryptogenic stroke. The aim of this study is to identify patients who are most likely to benefit from preventive treatments for PFO-related stroke recurrence, such as PFO closure. The study is to test other factors that may influence probability that PFO is the cause, such as patients’ clinical, radiographic and echocardiographic characteristics [36]. It was postulated earlier that to show the benefit of PFO closure, the PFO must be the cause of stroke, not an incidental finding [13, 34, 36]. Other factors such as occult atrial fibrillation, sub-threshold aortic atheroembolic disease, and coagulation disorders must be excluded. Silent atrial fibrillation is not easy to detect. Patients with cryptogenic stroke should be screened with electrocardiogram (ECG) monitoring for a longer time, as the detection of arrhythmia is difficult. Recently, brief intermittent long-term ECG recordings at regular time intervals were more effective than short-term continuous ECG in atrial fibrillation diagnosis [37]. Also, subclinical atrial tachyarrhythmias, without clinical atrial fibrillation, significantly increase the risk of ischaemic stroke or systemic embolism [38]. Presence of multiple risk factors (hypertension, diabetes, smoking, obesity, heart failure) may contribute to lower propensity of PFO to be the cause of stroke. Hopefully, the ongoing randomized trials REDUCE (with Hexel septal occluder), PC-Trial (with Amplatzer PFO occluder), RESPECT (with Amplatzer PFO occluder) and CLOSE (with any device) will provide a final answer whether closing is the right strategy [39].

We must keep in mind that invasive procedures are associated with periprocedural risk. There were rarely described serious complications with PFO closure such as tamponade, embolization with device or milder transient supraventricular arrhythmia or atrial fibrillation [32, 40, 41]. Also in observational studies the periprocedural risk was reported as low [42]. In the MIST randomized trial periprocedural complications were reported in up to 11% of patients.

The frequency and causes of surgical explantation of PFO closure devices were evaluated in a multicentre survey. More than 13 000 closures were performed in 9 years. Only 38 devices (0.28% [95% confidence interval: 0.20% to 0.37%]) required surgical removal. There was a wide range of causes cited for these removals. The most common reason for explantation was chest pain (n = 14), often determined to be secondary to nickel allergy to the PFO device. Other reasons for explantation included persistence of a residual shunt (n = 12), the presence of thrombus on the device (n = 4), pericardial effusion (n = 2), perforation of the atrium or aortic root (n = 2), recurrent strokes (n = 1), the development of endocarditis (n = 1), and undocumented reasons (n = 2). The frequency of removal seems to be device-dependent: in this survey the rate of explantation was 1 in 126 for CardioSEAL devices, 1 in 480 for Amplatzer devices, and 1 in 600 for the Helex device [43].

The closing strategy leads to increased risk of infective endocarditis 6 months after the procedure and potentially increased risk of bleeding during aspirin or double antiplatelet or warfarin therapy at least 3 months after the procedure.

According to the American Heart Association and American Stroke Association, for patients with an ischaemic stroke or TIA and a PFO, antiplatelet therapy is reasonable (class Ila; level of evidence B) and there are insufficient data to make a recommendation regarding PFO closure in patients with stroke and PFO (class IIb; level of evidence C) [44, 45]. Also physicians should be encouraged to enroll patients in clinical randomized studies.

**Migraine**

Migraine is a new potential indication for PFO closure. Patent foramen ovale and migraine were suspected to be linked when improvement in the frequency and severity of symptoms was observed after PFO closure for other reasons [46]. As in cryptogenic stroke, there is still no hard evidence for the PFO closing strategy in migraine. There are several reasons why it is difficult to show the efficacy...
of new treatment. Migraine is known for its spontaneous variability and for a placebo response rate of around 20-30% in well-conducted contemporary clinical trials. The response rate to preventive medications is about 50%. Most observations that closing PFO cures migraine were in patients after stroke, an event which may alter the course of migraine per se. Also medication used in some studies after PFO closure, that is aspirin [47, 48] and clopidogrel, show a small effect on migraine. Nonetheless, migraine symptoms were reduced in 75% of patients after PFO closure for different reasons [49]. The positive effect was observed regardless of residual shunt and was more pronounced in migraineurs with aura [49-52].

Decrease in migraine frequency after stroke and before PFO closure was found in a small group of patients [53]. The authors hypothesize that the results found after device implantation were confounded by the natural history of migraine. But they also observed further decline after closure. They speculated that it could be also due to aspirin after stroke [53].

Unfortunately, the randomized trial MIST failed to show a significant difference between medical and closure strategies. The problem needs more studies because of methodological problems reported in this trial [54]. There are two remaining trials actively randomizing patients: Percutaneous closure of PFO in Migraine with Aura (PRIMA), and Prospective Randomised Investigation to Evaluate incidental closure of PFO in Migraine with Aura (PRIMA), and remaining trials actively randomizing patients: Percutaneous closure of PFO in Migraine with Aura (PRIMA), and Prospective Randomised Investigation to Evaluate incidental closure of PFO in Migraine with Aura (PRIMA), and Prospective Randomised Investigation to Evaluate incidental closure of PFO in Migraine with Aura (PRIMA), and Prospective Randomised Investigation to Evaluate incidental closure of PFO in Migraine with Aura (PRIMA), and Prospective Randomised Investigation to Evaluate incidental closure of PFO in Migraine with Aura (PRIMA). Hopefully they will provide an answer.

**Decompression illness**

Patent foramen ovale was 2 to 6 times more frequent in a population of divers with decompression illness than in the general population [55]. However, as yet it is not assumed to be the cause of decompression illness. Many divers suffer from decompression disease without PFO being present. Many with PFO were symptomless. Even if decompression illness is associated with PFO, the risk is low because decompression illness is rare. In most cases symptoms are mild and entirely reversible with treatment. The Diver Alert Network says diving does not cause stroke, but it does expose individuals to elevated partial pressures and elevated hydrostatic pressure. A 2001 study reported in the *Journal of Occupational Health* concluded that a group of Japanese divers who held their breath during a technique called free diving appeared to be at increased risk for cerebral injuries with symptoms similar to those common in stroke victims. The researchers discovered that 13 of 16 divers in the study had histories of stroke-like neurological symptoms. None of the divers had vascular disease or risk factors for stroke. The symptoms occurred during or after repetitive deep dives [56]. Decompression illness in recreational divers is extremely rare, occurring after only 0.005% to 0.08% of dives, according to Divers Alert Network Annual Diving Report 2007 – 4 cases of decompression sickness (DCS) in 14,000 dives. Because it is so rare, screening for PFO in recreational divers is not recommended. A safe strategy would be to reduce the venous bubble load, because bubbles are the cause of decompression illness. This can be accomplished by avoiding dives that require decompression stops, by limiting bottom time, or by appropriate use of oxygen-enriched breathing mixes [57]. On the other hand, assessment of PFO is often recommended for divers with severe or recurrent neurological decompression sickness, especially when they occur with a safe diving protocol. Some divers who wish to return to unrestricted diving choose to have the PFO closed, but a careful discussion of risks and benefits is needed before this procedure can be recommended [57, 58]. Every patient should be treated individually, with detailed risk assessment.

**Conclusions**

There is a possibility that some patients with cryptogenic stroke, some with migraine with aura and some with decompression illness might benefit from closure of PFO, but there is little evidence that a routine closure strategy is appropriate. Even more careful indication assignment to the closing strategy in patients with cryptogenic stroke is essential, especially exclusion of other possible causes of stroke such as subclinical atrial fibrillation. The randomized trials, when completed, may provide the answer “to close or not to close”.

**References**


