"Migraine side effect" and stroke recurrence in late follow-up after transcatheter patent foramen ovale closure as secondary prevention of cryptogenic thromboembolism

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A b s t r a c t

Introduction: Patent foramen ovale (PFO) is associated with cryptogenic strokes, recurrent transient neurologic deficits, sleep apnea, decompression illness and migraines with aura.

Aim: We verify cryptogenic embolism recurrence after transcatheter PFO closure in patients younger than 55 years old, and determine the prevalence of migraine with aura before and after PFO closure.

Material and methods: We sent a questionnaire concerning the recurrence of stroke or transient ischemic attack (TIA) and the presence of migraine symptoms before and after PFO closure to 224 consecutive patients (mean age 40.9 ±9 years; 103 men; 108 patients < 40 years old, 116 patients 40–55 years old) after successful PFO transcatheter closure as secondary prevention of cryptogenic embolism.

Results: The mean follow-up period was 37.8 ±32.5 (median 27) months. Stroke or TIA recurred in 6 patients (2.6%), all of whom were over 40 years old at the time of closure. The median time of recurrence was 24 months. Two patients (0.89%) died, but the deaths were not related to the device nor to thromboembolism. Migraine occurred in the study group before closure in 68 (30.4%) patients. After the procedure 55 (80.9%) reported improvement or disappearance of migraine symptoms.

Conclusions: Recurrent strokes after PFO closure are rare, and they occur more often in patients over 40 years old at the time of closure. The PFO closure results in migraine subsiding or symptoms noticeably ameliorating.

Introduction

Foramen ovale allows blood shunt from the right to left atrium in foetus circulation. Birth entail formation of fosa ovalis or patent foramen ovale (PFO), a physiological remnant of foramen ovale, is a potential connection between the atria. The PFO present in 20–27% of the population in autopsy studies but only in 10–15% of patients in contrast-enhanced transesophageal echocardiography (TEE), which seems to be a normal variant [1].

The PFO is associated with cryptogenic strokes, recurrent transient neurologic deficits, sleep apnoea, decompression illness, and migraines with aura [2].

The PFO and migraine are linked because the prevalence and severity of migraine symptoms decreases after PFO closure due to other causes [3]. The migraine symptoms ameliorate also after PFO closure in uncontrolled studies [4].

Migraine with aura implies a new potential indication to PFO closure. A few theories (PFO theory among them) relate stroke and migraine [5]. The PFO demonstrates twice the prevalent in patients with migraine, and migraine is twice as common in PFO patients than in controls [4, 6]. Population studies [7–11] and three meta analyses [5, 12–14] reveal that migraine roughly doubles the risk for ischaemic stroke: the higher the incidence of migraine attacks, the grater increase in risk [15, 16]. Despite the doubled relative risk in migraine sufferers for ischaemic stroke, in absolute terms stroke remains a rare event in people with migraine, particularly in young individuals [5].

The hard evidence that closure exceeds pharmacological strategy in secondary prevention of stroke or migraine treatment is lacking because of short follow-ups in randomised studies, randomisation bias (the large number of off-label closures), and difficulties with indication assignment for the closing strategy [17]. Conflicting data have come from several randomised versus numerous observational trails [18, 19].

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Nevertheless, in our centre we prefer the closing strategy. We follow-up a significant number of patients after the PFO transcatheter procedure. We conducted the study to show long-term safety of the closing strategy, especially because rare but severe late adverse events after PFO or atrial septal defect (ASD) closure have been reported [20, 21].

Aim

We verify cryptogenic embolism recurrence after transcatheter PFO closure in patients younger than 55 years old, and determine the prevalence of migraine with aura before and after PFO closure.

Material and methods

The study group consisted of 224 consecutive patients (mean age 40.9 ±9 years) who underwent transcatheter PFO closure between 1999 and 2011 as secondary prevention of cryptogenic thromboembolism. Most of the patients who had their PFO closed were after stroke, one suffered from peripheral embolism of a subclavian artery,

Table I. Study group characteristics

Data, variables	No. of patients
Indication to closure:	
One stroke	178
Multiple strokes	3
TIA	41
Peripheral embolism	1
Decompression illness	1
Age [years]:	
< 40	108
40–55	116
Gender:	
Male	103
Female	121
Stroke potential risk factors:	
Smokers	49
Overweight BMI 25–30 kg/m^2	61
Obese BMI > 30 kg/m^2	15
Cholesterol LDL level > 3 mmol/l	67
Hypertension > 140/90 mm Hg	68
Diabetes	1
Device type:	
Amplatzer	218
CARDIA	6
Lost to follow-up	33

Table II. Treatment options after procedure

Years	Treatment
1999–2003	At least 6 months aspirin (ASA)
2004–2006	At least 6 months ASA + clopidogrel
2007–2011	3–6 months ASA + clopidogrel

and one had multiple events of decompression illness. Stroke risk factors presented in about one third of the group (Table I). Patients with at least 3-month follow-up were included in the study. All patients had transthoracic echocardiography performed the day after closure and 3 months after the procedure, and most patients were followed at month 12 after closure in outpatient settings and underwent electrocardiography (ECG) and transthoracic echocardiography (TTE).

We sent a questionnaire concerning the recurrence of stroke or TIA and the presence and intensity of migraine symptoms before and after PFO closure. We asked questions about diagnosis with migraine with aura, which were set by a neurologist. Patients suspected of stroke or TIA were invited to undergo additional tests in an outpatient department (clinical evaluation, TTE, ECG obligatory and TEE, neurological examination if indicated).

Every patient received antithrombotic treatment after the procedure (Table II). There were 33 (14.7%) patients lost for the follow-up.

Results

The mean follow-up period was 37.8 ±32.5 (median: 27) months (range: 3–151 months).

Stroke or TIA recurred in 6 patients (2.6%) (stroke – 5 patients, TIA – 1 patient), all of whom older than 40 years at the time of closure. The median time of recurrence was 24 months (range: 7–46 months), and it was significantly more prevalent in older patients (41–55 years) than in younger ones (< 40 years) (2.6% vs. 0%, log rank, Mantel-Cox, *p* < 0.02) (Figures 1, 2).

Only 1 patient, who suffered from cryptogenic stroke two years after the procedure and was 49 years old at the time of closure, was a migraine sufferer. Residual shunt as the cause of stroke was excluded.

Two patients (0.89%) died. One of them (39 years old at the time of closure) died in an accident 5 years after closure and the other (47 years old) had a myocardial infarction 6 years after closure (Figure 1).

Migraine with aura occurred in the study group before PFO closure in 68 (30.4%) patients: 19 (27.9%) men
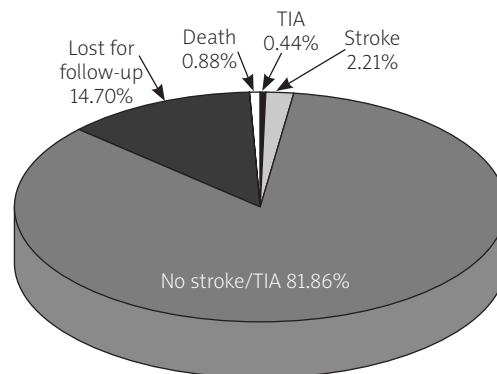

Figure 1. Recurrences of stroke and TIAs

and 49 (72%) women. The mean age in the subgroup was 40.3 ±8.9 years. The mean follow up in the subgroup was 38.6 ±31.7 months (range: 3–151 months, median: 28 months).

After the procedure 55 patients (80.8%) reported a noticeable improvement (expressed as lower incidence or severity of migraine attacks, in patients' subjective opinion) or disappearance of migraine symptoms. There were 13 patients (19.1%) without improvement. The difference was statistically significant ($p < 0.0001$).

Discussion

Cryptogenic stroke represents up to 40% of all ischaemic strokes [22]. Thorough investigation of the established causes of stroke settles diagnosis of exclusion.

Paradoxical embolisation seems the most likely mechanism of cryptogenic stroke through the PFO, but studies suggest other possible hypotheses such as the formation and release of thrombus from within the PFO tunnel or the passage of vasoactive humoral substances (that are normally degraded in pulmonary circulation) [23]. Retrospective, case-controlled studies have shown a higher prevalence of PFO in patients with cryptogenic stroke [24].

The extent of PFO-related stroke risk in the population still remains controversial [25]. A cause-effect relationship between PFO and cryptogenic stroke has not been convincingly demonstrated. Furthermore, several studies have consistently found that the presence of a PFO does not inherently increase the risk of recurrent stroke [22, 26–30]. This may be due to 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 annualised risk across studies of approximately 2%) [28, 29].

In a recently published study, with a mean follow-up period of 15 years (in 86 patients, less than 75 years old at the time of enrolment), the recurrent risk for stroke was rather high: 15% after a mean period of 4.9 years, reflecting a calculated event rate of 0.98% per year in this cohort [31]. 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). Most patients in this study were treated medically (only three underwent intervention therapy) [31]. In another study of 280 patients, with a 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 [32]. In a long-term follow up (mean 34 ±23 months) of 405 patients after HELEX septal occluder the annual stroke rate was 1.2% [33].

In our study stroke recurrence was rare, was observed in patients older than 40 years at the time of closure, and
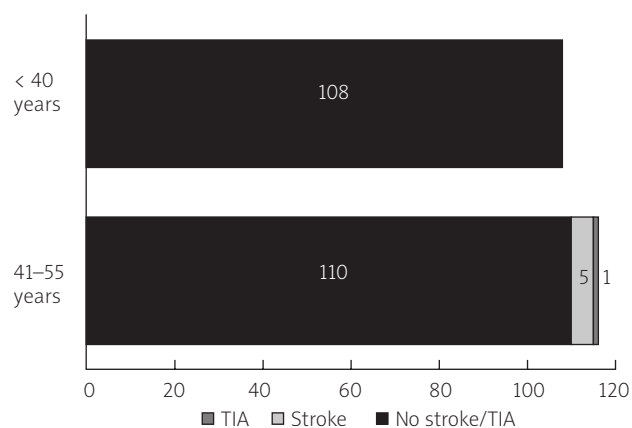

Figure 2. Recurrences of stroke and TIA in younger and older patients

had no association with the residual shunt or device-related abnormality.

A meta-analysis of observational, non-randomised trials gave conflicting results for a randomised (CLOSURE I) trial [34, 35]. In the observational studies, the incidence rate of recurrent stroke was 0.36 (95% confidence interval (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 almost four times higher (1.34; 95% CI: 0.69–2.34) and did not differ from the medical treatment.

The observational studies (incorporated 10 times more patients) favour closing PFO in secondary prevention of cryptogenic stroke. Randomised studies (CLOSURE I, RESPECT, and PC-trial) failed to show superiority of any particular closing strategy [18, 19, 34]. Reasons for failure may be as follows: I) a lower event rate than previously reported in the medical arm (lower baseline risk in the CLOSURE I trial); II) higher event rates in the closure arm that reflect unrealistic estimates in observational studies (the authors are less keen to publish unfavourable results); III) the lack of selection of high-risk patients with PFO-related events in randomised trials; and IV) too short (2 years) follow-up not fully capturing the benefit of the intervention. High-risk patients with clinical indicators of paradoxical embolism (large shunt, associated atrial septal aneurysm, Valsalva manoeuvre at stroke onset, evidence of deep vein thrombosis, evidence of a hypercoagulable state, stroke recurrence despite antithrombotic treatment, multiple clinical cerebrovascular events or multiple ischaemic lesions on brain magnetic resonance imaging (MRI), and absence of any conventional stroke risk factors) were probably more often treated with closure off-protocol and were not included in randomised trials [36–38].

We do not recognise the long-term risk after PFO closure. Since reports of rare but severe adverse events, such as device erosion, researchers have postulated the

formation of a registry and a focus on long-term safety of ASD or PFO device closure [21].

Observational studies report low periprocedural risk. Severe early complications like tamponade, embolisation with device, milder transient supraventricular arrhythmia, or atrial fibrillation present rarely [34, 39–41]. But in the MIST randomised trial, periprocedural complications were reported in up to 11% of patients, which seems high in relatively healthy patients with migraine.

The prevalence and causes of surgical explantation of PFO closure devices evaluated in a multicentre survey (more than 13,000 closures performed in 9 years) showed only 38 devices (0.28%, 95% CI: 0.20–0.37%) removed surgically. Chest pain, often determined secondary to nickel allergy, was revealed as most common cause. Other causes included persistence of a residual shunt, the presence of thrombus on the device, pericardial effusion, perforation of the atrium or aortic root, recurrent strokes, and the development of endocarditis. The removal prevalence seems device-dependent; the rate of explantation was 1 in 126 for CardioSEAL devices, 1 in 480 for Amplatzer devices, and 1 in 600 for Helex devices [20].

No patient in our study required device removal during follow-up.

The closing strategy increases the risk for infective endocarditis 6 months after procedure as well as bleeding risk during aspirin or double antiplatelet or warfarin therapy at least 3 months after the procedure. In our group we did not observe infective endocarditis or bleeding.

The migraine and stroke link in literature exists only in younger patients [14, 16, 42] and it associates more in women than in men, because migraine is more common in women. In our study, migraine proved three times more prevalent in patients with cryptogenic stroke or TIA than in the general population (30% vs. 10%). The gender distribution in the study agreed with population data. The theories, but not evidence, of a link between stroke and migraine are based on the following: the hypothesis of the occurrence of a migrainous infarction (the decrease in blood flow related to the aura reaches the ischaemic level or leads to dissection), the hypothesis of treatment (used to acutely abort migraine attacks, particularly vasoconstrictors increasing the risk for stroke), the hypothesis of risk factors (an increased prevalence of vascular risk factors in patients with migraine), the hypothesis of cortical spreading depression (the low threshold for cortical spreading depression that characterises the brain in migraine also lowers the threshold for cerebral ischaemia) [5].

The first PFO and migraine link was shown when an improvement in the prevalence and severity of symptoms was seen after PFO closure from other causes [3]. Similarly to cryptogenic stroke, hard evidence is lacking to show that the closing PFO strategy can contribute to healing migraines. Several causes make it difficult

to show the efficacy of the new treatment. Migraine is known for its spontaneous variability and response rate to preventive medications in about 50% of cases as well as in around 20–30% for placebo (in well conducted contemporary clinical trials). Most observations that closing PFO cures migraine were in patients after stroke, an event that may alter the course of migraine per se. Also, medications used in some studies after PFO closure, e.g. aspirin [43, 44] and clopidogrel, exert little influence on migraine. Nonetheless, our results support data that show migraine symptoms are reduced in at least 75% of patients after PFO closure due to different causes [45]. In the literature, this positive effect was more pronounced in migraine sufferers with aura, and was observed regardless of residual shunt [45–47].

In one small group of patients after stroke, the decrease in migraine prevalence was due to stroke and was enhanced by device closure [48].

We could not distinguish whether the amelioration of symptoms was the result of closure or part of the natural course of migraine after stroke.

Unfortunately, the randomised MIST trail failed to show any significant difference between the medical and the closure strategy in migraine treatment. The problem needs more studies to be carried out [49].

The study is retrospective and non-randomized. We included only successful closures of PFO in secondary prevention of thromboembolism to follow up. We lack almost 15% of patients follow-up data. The data about current pharmacological treatments are limited. Also some neurological data about type of stroke lacks. Patients were referred from different neurological hospitals, and not all neurological data were available.

Conclusions

Recurrent strokes after percutaneous PFO closure with septal occluder are rare and probably not related with PFO, they occur more often in patients older than 40 years at the time of closure. The PFO closure seems effective in secondary prevention of cryptogenic stroke, in patients younger than 40 years, but is less beneficial in older patients. Migraines are seen more often in patients with PFO than in the general population, and their gender prevalence is consistent with the population. Percutaneous PFO closure with a septal occluder results in migraines subsiding or symptoms noticeably ameliorating in a significant percentage of patients.

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