Seven-year follow-up of percutaneous closure of patent foramen ovale

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Background: Observational studies favor percutaneous closure of patent foramen ovale (PFO) over medical treatment to reduce recurrent stroke while randomized trials fail to demonstrate significant superiority of percutaneous PFO closure. Few long-term studies are available post PFO closure. This study reports long-term clinical outcomes after percutaneous PFO closure.

Methods: Between 1997 and 2006, 86 consecutive eligible patients with cerebrovascular events, presumably related to PFO, underwent percutaneous PFO closure. All 86 patients were invited to a long-term follow-up, which was carried out during 2011 and 2012. Results: Percutaneous PFO closure was successfully performed in 85 of 86 patients. The follow-up rate was 100%. No cardiovascular or cerebrovascular deaths occurred. Two patients (both women) died from lung cancer during follow-up. Follow-up visits were conducted for 64 patients and the remaining 20 patients were followed up by phone. The mean follow-up time was 7.3 years (5 to 12.4 years). Mean age at PFO closure was 49 years. One patient had a minor stroke one month after PFO closure and a transient ischemic attack (TIA) two years afterwards. One other patient suffered from a TIA six years after closure. No long-term device-related complications were observed. Conclusions: Percutaneous PFO closure was associated with very low risk of recurrent stroke and is suitable in most patients. We observed no mortality and no long-term device-related complications related to PFO closure, indicating that percutaneous PFO closure is a safe and efficient treatment even in the long term.

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1. Introduction

A patent foramen ovale (PFO) is a common heart defect and is present in about 25% of the general population [1]. An association between PFO and cryptogenic stroke (CS) in young adults has been shown in several studies. Furthermore, a relationship between increased risk for recurrent thromboembolic events, PFO and CS has previously been reported [2–5]. PFO and atrial septal aneurysm (ASA) have been reported to be associated with an increased risk of recurrent thromboembolic stroke, and a large PFO is a predictor for cerebrovascular ischemic events [6–9]. Potential therapeutic strategies for secondary prevention of paradoxical embolic stroke include long-term oral anticoagulation or antiplatelet medication, surgical PFO closure, and percutaneous PFO closure with a catheter-based procedure using a septal occluder device. Percutaneous PFO closure has been shown to be safe and feasible [10–13]. Several different devices and different regimens of antiplatelet or anticoagulant therapy are used at present. Five observational trials have indicated that PFO closure by device lowers the relative risk of recurrent cerebrovascular events by almost 80% compared to medical treatment [14–18]. In addition, three randomized trials (CLOSURE I, RESPECT and the PC Trial) have thus far been published [19–21]. CLOSURE I showed no significant benefit of device closure over medical therapy during two years of follow-up. The primary outcomes of the most recent trials, RESPECT and the PC Trial, were not significantly affected by which treatment was given. There are few studies reporting long-term clinical outcomes of device closure and, given the relatively low yearly rate of recurrent stroke (1–2%) [22,23], there is a need for much larger follow-up studies, either by recruiting more patients or by maintaining a longer follow-up period. The number of patients lost to follow-up has to be kept to a minimum, especially when the event rate is low, to avoid giving misleading results. The aim of the present study was to provide a long-term clinical follow-up of patients with a previous percutaneous closure of their PFO as secondary prevention after a cryptogenic stroke, by monitoring survival, complications, recurrence and other clinical significant conditions.

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2. Methods and patients

2.1. Patient selection

Between 1997 and 2006, 86 consecutive patients (47 men and 39 women) were referred to our center for PFO closure. All these patients were diagnosed with cryptogenic stroke or transient ischemic attack (TIA) associated with PFO by neurologists and cardiologists at local hospitals before they were referred. Patients were referred from hospitals in central and western part of Sweden. Due to the complexity of cryptogenic stroke and PFO, further evaluation of the patient’s clinical data and medical records, including transesophageal echocardiography (TEE), computerized tomography (CT) scan or magnetic resonance imaging (MRI) of the brain, was made by our interventional cardiologists, who took the final decision about PFO closure after consulting the TEE imaging expert and stroke expert.

For both index stroke/TIA and at follow up, a diagnosis of TIA was given by the treating neurologist if acute neurological deficits with a probable vascular (ischemic) cause completely resolved within 24 h. Ischemic stroke was defined as a sudden new focal neurologi cal deficit lasting more than 24 h [24]. Stroke etiology was defined according to the modified TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria [25].

Patients with stroke of known origin, such as cardiac events (atrial fibrillation (AF), acute myocardial infarction within the previous four weeks, or large apical infarction at any time), patients without PFO, and patients with major aortic plaques, as well as patients with decerebration, illness or ortho doxa–platyptea, were excluded from the study. If other probable causes of stroke (as described above) had been ruled out by adequate imaging and biochemical testing, the cerebrovascular event was considered cryptogenic and related to PFO if the presence of a PFO with or without ASA was established.

The main criteria for closure were patients with at least one cryptogenic stroke with high-risk morphology (PFO with ASA) or recurrent cryptogenic stroke and a PFO without ASA. The present study was approved by the regional ethics review board in Gothenburg, Sweden and all patients gave written informed consent.

2.2. PFO closure

Closure of the PFO guided by a perioperative TEE was performed under general anesthesia and the Amplatzer® PFO Occluder device (AGA Medical Corp, Plymouth, MN, USA) was used in all patients who underwent PFO closure. Right-to-left shunting, at rest or during the Valsalva maneuver, was detected in all patients by TEE before the PFO closure.

Intra-procedural catheter-related complications were defined according to Khairy et al. [26]. Major complications were defined as death, hemorrhage requiring blood transfusion, cardiac tamponade needing surgical intervention, and massive fara pulmonary emboli. Minor complications were defined as bleeding not requiring transfusion, periprocedural atrial arrhythmias, transient atrioventricular node block, device arm fractures, device embolization with successful catheter retrieval, asymptomatic device thrombosis, need for recatheterization, symptomatic air embolism, transient ST-segment elevation, arteriovenous fistula formation, and femoral hematoma.

2.3. Follow-up

All patients were examined six months after PFO closure by the interventional cardiologist to assess periprocedural complications and clinical status. A TEE was also performed at six months after PFO closure with color Doppler and contrast injections during the Valsalva maneuver in all patients. TEE was repeated every six months in patients with residual substantial shunting. Residual shunting was defined as small when 1–20 bubbles were seen in the left atrium or when the shunt was seen only with color Doppler, despite multiple contrast injections during the Valsalva maneuver. When more than 20 bubbles were seen in the left atrium, the shunt was considered substantial [27].

Patients with residual shunting continued with anticoagulation treatment until complete closure of PFO occurred. After six months, no routine follow-up was carried out by our unit; follow-up was entirely left to the referring physician. No recommendations regarding medical treatment were made at the time of our termination of follow-up.

During 2011 and 2012, all surviving patients were invited to long-term clinical follow-up and personal interviews. A structured medical history including items on recurrent stroke/TIA, risk factors for stroke and potential complications to percutaneous treatment was obtained for all patients. Patients who agreed to attend follow-up at our center were examined with electrocardiogram (ECG) and transthoracic echocardiography (TTE). The patient’s neurological status was assessed using the modified Rankin Scale [28–30]. Patients who could not attend our center were followed up with a structured telephone interview. No patient refused follow-up.

Information about recurrent stroke/TIA was obtained from medical records of patients if they were admitted at any hospital for a new clinical event of ischemic stroke or TIA after PFO closure. Informed consent was given by all patients for access to their medical records from all clinics where they had been treated during the follow-up for suspect events. All relevant medical records and documentation of imaging procedures were collected.

Vital status was ascertained from hospital records, public civil registries and the Swedish Cause of Death Register (CDB) [31]. Information on the two patients who had died during follow-up was obtained from hospital records.

2.4. Statistical analysis

Distributions are presented as mean and standard error of the mean. Event-free survival was displayed by a Kaplan–Meier plot. Statistical analyses were performed using PASW Statistics for Windows, Version 18.0 software (IBM Corporation, Armonk, NY, USA).

3. Results

No patients died from cardiovascular causes. Two patients died of lung cancer at 39 and 60 months after PFO closure, respectively. Both of these patients were free from recurrent events before death.

The long-term follow-up was successfully performed in all the 84 live patients (follow-up rate 100%). Sixty-four patients attended the follow-up visit. Twenty patients did not attend but were followed up by a structured telephone interview and retrieval of hospital records. Fourteen of these patients were living far away from our site and six patients lived nearby but were unwilling to come to the clinic for an examination. The follow-up was performed within a mean of 7.3 years (minimum 5.0 years – maximum 12.4 years) after the PFO closure, corresponding to an accumulated follow-up of 616 patient years. The mean follow-up after the index stroke or TIA event was 13 years (range: 6–20 years).

Prior to closure, 68 patients in this study (79%) had CT or MR data corresponding to the current stroke or TIA symptoms before closure. Sixty-one patients (71%) had PFO with ASA and 25 patients (29%) had PFO without ASA. Forty-eight patients (56%) had first-time stroke/TIA while 38 (44%) had recurrent stroke/TIA. Further information on patient characteristics and medication at closure and at follow-up are displayed in Table 1.

PFO closure with an Amplatzer device was performed successfully in 85 of 86 patients. One patient with several septal defects was not suitable for percutaneous closure and remained on lifelong treatment with warfarin. Fig. 1 shows indications for PFO closure in this study.

Mean age at PFO closure was 49 years and at follow-up 56 years. No cardiovascular or cerebrovascular deaths related to the device closure occurred. At the time of the index event, 61 of the patients had a PFO with ASA. One patient with a significant carotid stenosis was considered by the neurologists to have a high risk of paradoxical embolism and the index event was considered to be caused by fragmented thrombus; therefore, the patient underwent closure. This patient was event free at follow-up and the carotid stenosis was not of any clinical relevance; therefore, the patient was not operated on but only medicated with 75 mg acetylsalicylic acid.

Scoring MRS at follow-up, 78 patients (90%) had a good MRS score of 0–1 (0 = no symptoms at all; 1 = no significant disability despite symptoms, able to carry out all usual duties and activities). Six patients (8%) scored 2–3 (2 = slightly disability, unable to carry out all previous activities, but able to look after own affairs; 3 = moderate disability requiring some help, but able to walk without assistance).

3.1. Recurrent stroke or TIA

In this long-term study, two patients (2%) suffered from a recurrent neurologic event, giving a rate of three neurologic events per 1000 patient-years (PY). Of the two patients with recurrent events, one patient reported having severe migraine headache preoperatively and she suffered an MRI-verified ischemic stroke one month after PFO closure at the age of 36. However, the same patient suffered a TIA (without CT or MRI evidence of new cerebral lesions) two years after closure. The other patient suffered a TIA (without CT or MRI evidence of new cerebral lesions) six years after closure. He had cardiovascular risk factors including age (72 years at the time of the recurrent event), hypertension, and an elevated BMI of 28. Both neurological events occurred in patients who had undergone successful PFO closure and had no evidence of thrombus formation or residual leaking during the follow-up. They had PFO and ASA before closure and complete PFO closure was
documented by TEE at the six-month follow-up. Both patients were on 75 mg acetylsalicylic acid at the time of recurrence. One patient with brain abscess and PFO was included in this study because the panel considered the event assuredly related to PFO. This patient had no more events during the time of follow-up.

Long-term event-free survival post PFO closure is shown in Fig. 2. No device-related or medical treatment-related complications were noticed in these two patients at the time of follow-up. Regarding the medication, as shown in Table 1, all 86 patients (100%) were on medical treatment, of whom 55 (64%) were on warfarin and 25 (29%) on acetylic acid. At long-term follow-up, only 51 (57%) were on medical treatment, of whom only two (2%) on warfarin and 46 (54%) on acetylic acid.

3.2. Complications

There were no procedure-related major complications during the implantation of the closure device. One patient with several septal defects was not suitable for percutaneous closure. Three patients (3.5%) suffered from AF during the first six months after PFO closure and this was converted to sinus rhythm by electrical cardioversion. One of these patients was still in AF at the six-month follow-up, but it was in due course converted such that the patient was in sinus rhythm at long-term follow-up. No further hospitalization was reported and this patient had no recurrent events.

No long-term complications related to PFO closure, such as death, device embolization, or chronic AF were found.

3.3. Echocardiographic follow-up

After a mean period of six months, the TEE showed complete device closure in 88% of patients. Eight patients (10%) showed a small shunt and two patients (2%) showed a substantial shunt. After 18 months, only six patients (7%) still showed small shunts and none showed substantial shunts. No device thrombus or device embolization was detected. At the long-term follow-up visit, a transthoracic echocardiography (TTE) was performed on 64 patients (74%) and no residual shunts were detected with color Doppler. No long-term device-related complications of PFO closure were observed.

3.4. Other observed events

AV block: One patient with PFO and ASA underwent PFO closure in May 2005 with a 35 mm Amplatzer device, and a pacemaker was inserted due to AV block III in December 2010 at the age of 70. One other patient who underwent PFO closure, also with a 35 mm Amplatzer device, at the age of 37 suffered AV block I and periodic AV block II (Wenckebach periodicity), which was observed at several hospital visits. This AV block I and II was asymptomatic and the patient had AV block I at time of long-term follow-up.

Migraine: 31% of patients reported migraine headache preoperatively, which reduced to 13% at follow-up. However, the aim of this study was not to investigate the prevalence of migraine headache, so this retrospective finding represents only patient recall.

4. Discussion

PFO closure in this long-term follow-up study of up to 12.4 years was associated with a very low recurrent event rate of 0.3% per year and a success rate of 99%. The 0.3% per year rate of recurrent neurological events in this study is lower than reported in a recently published meta-analysis of 48 studies, which showed a recurrence rate of 0.8% per year for PFO closure and 5% per year for pharmacologically treated PFO patients [32]. The rate of recurrent stroke/TIA in this study is essentially based on patient-reported events, as in the CLOSURE I and

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**Table 1**

Patient characteristics and medication at closure and at follow-up.

| Characteristics | No. (%) of patients |
|-----------------|---------------------|
|                 | At closure (n = 86)  | At long-term follow-up (n = 84) |
| Age (range)     | 49 ± 10.6           | 56 ± 10.44                     |
| Hypertension    | 15 (17)             | 20 (23)                        |
| Hyperlipidemia  | 15 (17)             | 22 (26)                        |
| Diabetes Mellitus| 2 (2)               | 2 (2)                          |
| Atrial fibrillation | 0 (0)             | 0 (0)                          |
| PVD             | 1 (1)               | 1 (1)                          |
| Current smoker  | 11 (13)             | 9 (11)                         |
| Medication      |                     |                                |
| Warfarin        | 55 (64)             | 2 (2)                          |
| Aspirin         | 25 (29)             | 46 (54)                        |
| Clopidogrel     | 1 (1)               | 0 (0)                          |
| Dipyridamol/+   | 4 (5)               | 2 (2)                          |
| Dipyridamol     | 0                   | 1 (1)                          |
| No medication   | 0                   | 33 (38)                        |

PFO: patent foramen ovale, PVD: peripheral vascular disease.
RESPECT studies, as well as any clinical symptoms that the investigators judged to be caused by cerebral ischemia. In order to study recurrent events accurately, we requisitioned patient records from the respective hospitals for patients with symptoms suggestive of recurrent events.

There are three randomized clinical trials on device PFO closure to date. The first study, CLOSURE I, showed no significant benefit of PFO closure on the primary end point to prevent recurrent stroke but had a trend towards a slight reduction in recurring TIA: 3.3% for PFO closure vs. 4.6% for medical therapy alone [19]. The RESPECT trial [20] and the PC Trial [21] have both been published recently and, as with the CLOSURE I study, their primary outcome was not significantly affected by which treatment was given. However, the results of these studies should be interpreted with caution because the event rate was lower than expected. Recruitment to the studies was very difficult and took more than eight years to accomplish; in the meantime, very large numbers of PFOs were closed off-label, which may lead to selection bias by excluding high-risk PFO patients. Furthermore, the high dropout rate compared to event rate in these studies makes interpretation of the intention-to-treat analysis of recurrence rate susceptible to error. The low recurrence rate of 0.3% per year in the present study is most likely explained by patient selection; we excluded patients with PFO and stroke that was not considered to be cryptogenic, due to the presence of ischemic heart disease, AF, arterial plaque or atypical neurologic symptoms. Approximately 30% of our referrals are accepted for PFO closure. Given the clear positive effects seen in observational studies [14-18], randomized trials of adequate size are urgently needed.

The present study provides true long-term follow-up and adds to our understanding of the long-term consequences of PFO closure in patients with a history of cerebrovascular events associated with PFO. The mean follow-up post PFO closure was 7.3 years, with a maximum of 12.4 years, and the mean time from index event to follow-up was 13 years. This is the first long-term clinical follow-up of PFO patients with a follow-up rate of 100%, and where the majority of patients seen at clinic visits were given a clinical examination including an echocardiogram. Two earlier studies have reported comparable follow-up periods but both had a lower follow-up rate. The mean follow-up in the study by Fischer et al. was 15.4 years but follow-up rate was only 89% post PFO closure [22]. The mean follow-up after index event in the study by Wahl et al. was 10 years with a mean follow-up rate of 98% [23]. When the event rate is low it is of high importance to have a high follow-up rate in order to eliminate the risk of bias.

There were no procedure-related major complications in the present study. The 3.5% incidence of AF was the only potentially procedure-related minor complication in the present study. However, the observed AF was transient and no chronic AF could be observed. The incidence of AF varies in other studies from 0.6% [33] to 7.6% [34] during the first year post PFO closure. In 2003, Khairy et al. reported 7.9% major complications and 1.5% minor complications [26] and in 2009 Wahl et al. reported a complication rate of 0.8% [33]. The reduction of complication rate over time is most likely a result of better patient selection, better devices and greater experience among interventional cardiologists, although the retrospective approach in the present paper might underestimate minor complications, such as minor bleeds.

PFO closure with the Amplatzer device has been reported to be associated with lower risk of device thrombus formation compared to other PFO occluding devices [35]. We found no thrombus formation on the Amplatzer occluder device.

In the present study, we had an 88% success rate for PFO closure with the Amplatzer device at six-month follow-up and 93% after a mean follow-up of 18 months, compared to 86.1% at six months and 86.7 at 24 months in the CLOSURE I study, which used the STARFlex device [19]. Minimal shunting observed in six patients (7%) in our study after 18 months was not considered to be of any clinical relevance and was not associated with recurrent events. Neither of the patients who had recurrent stroke nor TIA (2%) had any detectable residual shunting. No shunts were detected by TTE in the long-term follow-up.

The results of this study should be considered in the light of the following limitations. First, the diagnosis of paradoxical embolism remains presumptive and cannot be considered synonymous with cryptogenic stroke or TIA. Second, the patient population in this study is a selected group referred to our hospital in a non-randomized, retrospective, entitled order, without a control group, as in most case studies. Due to the lack of widely accepted guidelines on the management of PFO and cryptogenic stroke, 53% of patients in this study had discontinued their medical treatment (in agreement with their physicians). However, despite discontinuation of medical therapy, we did not observe more than 2% recurrent events.

5. Conclusions

In this long-term follow-up study of consecutive patients, percutaneous closure of PFO was associated with very low risk of recurrent stroke, no mortality related to cerebrovascular disease, and no short- or long-term device-related major complications, thus indicating that percutaneous PFO closure is a safe and efficient treatment option. Nonetheless, long-term randomized studies are needed to determine the efficacy of different therapeutic measures and the importance of patient selection.

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