

Long-term follow-up after closure of patent foramen ovale

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Summary

Background: Percutaneous patent foramen ovale (PFO) closure has been shown to be safe and feasible with a variety of devices, and its clinical efficacy appears favourable compared with medical treatment alone. However, long-term follow-up remains largely unknown. We report the late clinical results of our early experience with one of the first commercially available devices, the Sideris Buttoned Occluder.

Methods: Thirty-two patients (age 50 ± 12 years; 63% male; 28% atrial septal aneurysm) underwent PFO closure using the Sideris Occluder for secondary prevention of presumed paradoxical embolism.

Results: There were four procedural complications (13%), including two embolisations of the counteroccluder of the device with successful percutaneous removal in both cases, and one arteriovenous fistula requiring surgical repair. The implantation procedure failed in one patient (3%) because of laceration of the femoral artery, with ensuing retroperitoneal haematoma requiring surgical revision. None of these complications had long-term sequelae. Contrast transoesophageal echocardiography at 6 months showed complete closure in 55% of cases, and a minimal, moderate, or large residual shunt in 28%, 7%, and 10%, respectively. During a mean follow-up period of 12.3 ± 2.6 years (median 13 years; total 378 patient-years), one death, two ischaemic strokes, two transient ischaemic attacks (TIAs), and one peripheral embolism occurred. Survival free from recurrent ischaemic stroke, TIA, or peripheral embolism was 97% at 1 year, 90% at 5 years, and 84% at 10 years. There was one incident of atrial fibrillation.

Conclusions: Despite the high periprocedural complication and residual shunt rates, percutaneous PFO closure using the Sideris Occluder presented no long-term safety concerns. The rate of recurrent events 10 years after percutaneous PFO closure was low.

Key words: atrial septal aneurysm; patent foramen ovale; cerebral ischaemia; embolism; secondary stroke prevention

Introduction

The association of patent foramen ovale (PFO) with cryptogenic stroke, independently reported by Lechat [1] and Webster [2] in 1988, has been repeatedly confirmed [3, 4]. This observation has been extended to adults >55 years, with a significantly higher prevalence of PFO alone (28.3% vs 11.9%; odds ratio [OR] 2.9; 95% confidence interval [CI] 1.7–5.0; $p < 0.001$) as well as of

PFO associated with atrial septal aneurysm (ASA; 15.2% vs 4.4%; OR 3.9; 95% CI 1.8–8.5; $p < 0.001$) among patients with cryptogenic stroke compared with those with stroke of known stroke cause [5].

In patients with presumed paradoxical embolism, secondary prevention remains a matter of debate. Patients with cryptogenic stroke related to PFO are at risk for recurrence despite medical treatment, with yearly recurrence rates ranging from 0.6–12% [6, 7], a risk that may be particularly pronounced in patients with PFO and associated ASA [6, 8]. Nonrandomised data suggest the superiority of percutaneous PFO closure for secondary prevention of paradoxical embolism as compared with medical treatment alone [7, 9–11]. However, three randomised studies failed to confirm these results [12–14]. As the protocols of all three trials overestimated the incidence of recurrent events in both groups, data on long-term clinical

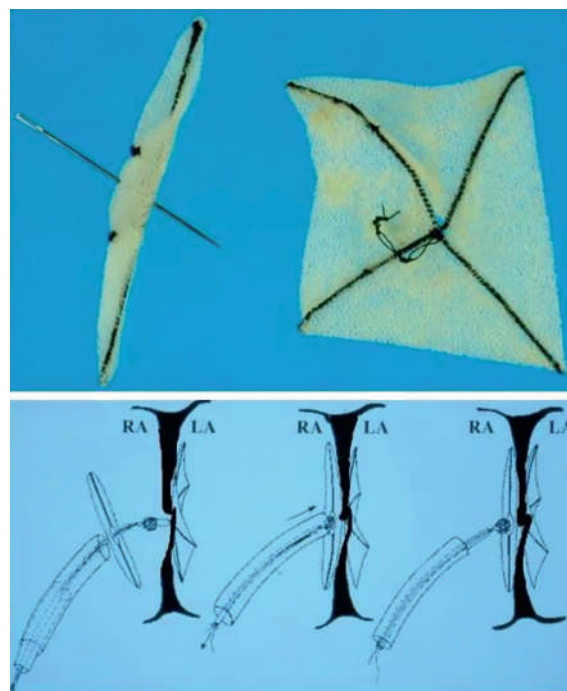


Figure 1: Sideris Buttoned Occluder (top) and implantation steps (bottom).

LA = left atrium; RA = right atrium

follow-up of such patients are still of interest. In this study we report the late clinical results (up to 15 years of follow-up) of our experience with one of the first commercially available devices, the Sideris Buttoned Occluder (SBO, fig. 1).

Methods

Patients

Between April 1994 and November 1999, 32 patients underwent percutaneous PFO closure with the SBO for secondary prevention of presumed paradoxical embolism. An embolic event was considered due to paradoxical embolism when the following criteria were fulfilled: presence of PFO with or without ASA with spontaneous or inducible interatrial right-to-left shunt during contrast transoesophageal echocardiography (TOE); clinically and/or radiologically confirmed ischaemic stroke, transient ischaemic attack, or peripheral embolism; and exclusion of any other conventional cause. The procedure was approved by the local Ethics Committee, and patients gave written informed consent.

Echocardiography

The diagnosis of PFO and ASA was based on contrast TOE, with aerated colloid solution injected into an antecubital vein at the end of a vigorous and sustained Valsalva manoeuvre. PFO was defined as flap-like opening in the atrial septum secundum, with the septum primum serving as one-way valve allowing for permanent or transient right-to-left shunt. ASA was diagnosed as an abnormally redundant interatrial septum with an excursion of >10 mm into the right or left atrium and a diameter at the base of the aneurysm of at least 15 mm [15]. Spontaneous or provoked right-to-left shunt was semiquantitatively graded according to the number of bubbles detected in the left atrium after crossing the interatrial septum on a still frame: grade 0 = none, grade 1 = minimal (1–5 bubbles), grade 2 = moderate (6–20 bubbles), and grade 3 = severe (>20 bubbles) [2]. In order to demonstrate unequivocally the presence of a PFO, care was taken to document the actual passage of contrast bubbles through the rent, but this was not possible in all cases.

Sideris Buttoned Occluder

The SBO (fig. 1) at the time was a polyester patch on a nitinol cross frame in the left atrium, retained by a polyester coated wire in the right atrium. It could be constrained within an 11 French (Fr) delivery system. The retaining wire was pushed over a nylon thread fed through a central hole in the polyester coat. The thread

featured a knot which prevented disengagement of the retaining wire, once it was advanced over the knot.

Percutaneous PFO closure

The interventions were performed under local anaesthesia and fluoroscopic guidance [16]. Intraprocedural guidance by TOE [17–19] or intracardiac echocardiography [20, 21] was not used in any case. However, all patients had undergone contrast TOE for initial diagnosis of PFO prior to the intervention.

After venous access was gained via the right femoral vein, the PFO was crossed under fluoroscopic guidance in the anteroposterior view either with a standard length regular 0.035 inch guidewire alone, or with the help of a catheter, typically a 6 Fr multipurpose catheter. Balloon sizing was not used. Indeed, the maximal opening of the flap-like PFO is not instrumental for the success of closure.

An exchange guidewire was placed through the catheter in the left atrium. The multipurpose catheter was withdrawn, and an 11 Fr delivery sheath was advanced over the guidewire in the left atrium. The SBO consisted of three components: occluder, counteroccluder, and delivery system. The occluder was folded and placed in the delivery sheath, and then advanced through the sheath using a pushing catheter until it appeared in the left atrium. The delivery sheath was then gently retracted to the right atrium. The counteroccluder was placed in the delivery sheath, over the delivery nylon thread connected to the occluder, and similarly delivered into the right atrium under fluoroscopic guidance. The occluder was pulled towards the counteroccluder and the counteroccluder gently pushed with the tip of the sheath over the knot portion of the occluder; the device was thus buttoned across the interatrial septum under fluoroscopic guidance. Finally, the loading wire was cut and withdrawn, thus disconnecting the implanted device from the delivery system.

The transeptal sheath was then used for a final contrast medium injection. The contrast can be followed through to the levophase to delineate the left atrial contour and device placement also. Finally, the sheath was removed and haemostasis achieved by manual compression. Patients were released to full physical activity as early as a few hours after the procedure. Trans-thoracic contrast echocardiography was performed before discharge in order to document correct and stable device position. Acetylsalicylic acid (100 mg) was prescribed once daily for 6 months for antithrombotic protection.

As reported in previous publications by our group, we performed systematic coronary angiography in patients undergoing percutaneous PFO closure aged

>50 in males and >60 in females. In this study, a rather high proportion of the examined patients (29%) presented with unsuspected coronary artery disease, justifying incidental coronary angiography in selected patients. Predictors were the age as well as the presence of conventional cardiovascular risk factors [22].

Follow-up evaluation

The outcome following the intervention was prospectively assessed for up to 15 years. A contrast TOE was repeated 6 months after percutaneous PFO closure. Thereafter, patients underwent structured telephone interviews, addressing recurrent embolic events, device related problems, and health status at regular intervals. Initial follow-up information was available for all patients, but two patients (6%) were eventually lost to follow-up.

Death, and recurrent ischaemic stroke, TIA, or peripheral embolism were considered endpoints. Patients with suspected recurrent cerebrovascular events were re-examined by a neurologist, and a new imaging study of the brain was performed.

Statistical analysis

An intention-to-treat analysis was performed considering all patients selected for implantation of a SBO

during the study period, including the patient in whom the implantation failed. Continuous variables are expressed as mean \pm 1 standard deviation, and were compared with a two-sided, unpaired *t*-test. Categorical variables are reported as counts and percentages, and were compared using the Fisher's exact test. Estimates for freedom from the composite of recurrent TIA, stroke, and peripheral embolism were obtained by means of the Kaplan-Meier method. Binary logistic regression analysis was performed to identify independent predictors of recurrence. Estimates of the hazard ratio (HR) and 95% confidence interval (CI) for each independent variable were obtained by proportional hazard regression analysis. Statistical significance was assumed with a *p*-value <0.05. All data were analysed with the use of SPSS software (version 15.0.1, SPSS Inc.).

Results

In-hospital outcome

Demographic data are summarised in table 1. In one patient (3%), the planned SBO implantation was aborted because of laceration of the femoral artery during initial insertion of the 11 Fr venous sheath with an ensuing retroperitoneal haematoma. Because of the absence of concurrent embolic causes in the extensive preinterventional work-up, surgical PFO closure was deemed reasonable by an interdisciplinary team and was performed concomitantly to the required vascular revision. This patient is doing well at 18 years of follow-up. All other 31 (97%) implantation procedures were successful.

Periprocedural complications, including the one described above, were observed in a total of four patients (13%). There were two cases of embolisation of the counteroccluder of the SBO with successful percutaneous removal. The occluder patch stayed in place in both. One patient who had undergone simultaneous coronary angiography developed an arteriovenous fistula at the puncture site requiring elective surgical closure. There was no in-hospital death, and none of the procedural complications resulted in long-term sequelae.

Total procedure time, including incidental coronary angiography [22] in 26 patients (81%), and an *ad hoc* percutaneous coronary intervention in two patients, was 71 ± 23 minutes (median 70 minutes). Total fluoroscopy time was 17 ± 8 minutes (median 14 minutes). One- vessel coronary artery disease was found in only three patients, one patient had coronary sclerosis without significant stenosis. In the six patients undergoing PFO closure only, total procedure time amounted to 48 ± 26 minutes (median 38 minutes).

Table 1: Baseline clinical characteristics.

Patients	32
Age (years)	50 \pm 12 (median 51; range 18–73)
Male gender	20 (63%)
Height (cm)	169 \pm 10
Weight (kg)	75 \pm 14
Atrial septal anatomy	
Left atrial size (mm)	38 \pm 7
Patent foramen ovale alone	23 (72%)
Patent foramen ovale and atrial septal aneurysm	9 (28%)
Cardiovascular risk factors	
Arterial hypertension	14 (44%)
Diabetes mellitus	4 (13%)
Smoking history	14 (44%)
Family history	14 (44%)
Total cholesterol (mmol/l)	5.6 \pm 1.0
Embolic index event	
Ischaemic stroke	17 (53%)
Transient ischaemic attack	12 (38%)
Peripheral embolism	3 (9%)
Number of clinically apparent prior embolic events	
One	18 (56%)
Two	9 (28%)
Three	2 (6%)
Four or more	3 (10%)

Complications were not significantly different in patients receiving small SBOs (<30 mm; n = 12) as compared with patients with large SBOs (≥30 mm; n = 20% vs 25%; p = 0.3), patients with an associated ASA (n = 9; 28% as compared with patients with an isolated PFO (n = 23; 72%, and 0% vs 21%; p = 0.3), or patients ≥55 years (n = 12; 37%) as compared with <55 years (n = 20; 73%, 9% vs 18%; p = 1.0).

Transthoracic contrast echocardiography after a Valsalva manoeuvre within 24 hours of percutaneous PFO closure, performed in all 31 patients with an implanted device, detected a residual shunt in eight patients (26%).

Late echocardiographic outcome

Contrast TOE after Valsalva manoeuvre at 6 months (fig. 2), performed in 29/31 (94%) patients with an implanted device, showed complete PFO closure in 16 patients (55%), and a minimal, moderate, or large residual shunt in 8 (28%), 2 (7%), and 3 (10%), respectively (fig. 3).

There was no significant difference regarding residual shunts with smaller (<30 mm; n = 12; 39%) or larger SBOs (>30 mm; n = 19; 61%, 42% vs 42%, respectively, p = 1.0), in older (≥55 years; n = 12; 39%) or younger patients (<55 years; n = 19; 61%, 50% vs 37%; p = 0.7), or PFO and associated ASA (n = 9; 29%) or isolated PFO (n = 22; 71%, 33% vs 45%, p <0.7). No thrombus was detected on the devices.

Late outcome

During 12.3 ± 2.6 years of follow-up (median 13 years, total 378 patient-years), one death, unrelated to a recurrent embolic event, two ischaemic strokes, two TIAs, and one peripheral embolism occurred (16%). One of

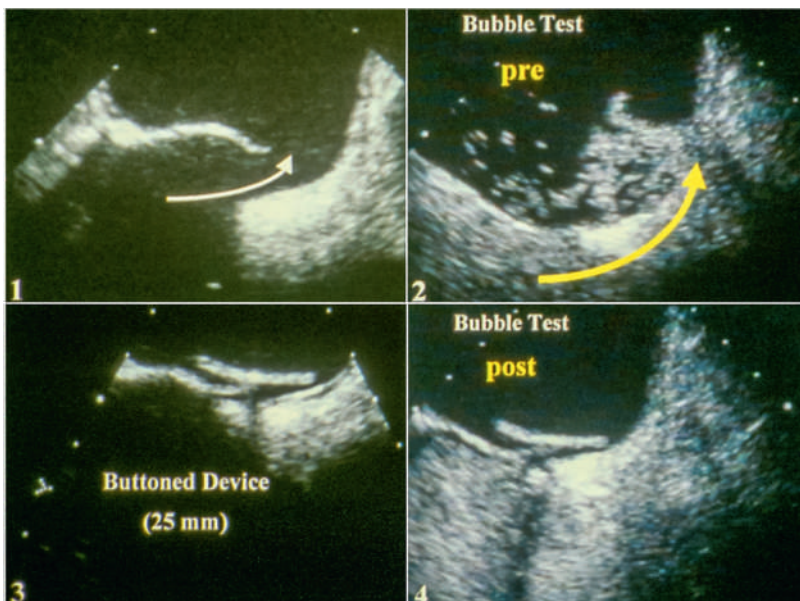


Figure 2: 1. Transoesophageal echocardiography of patent foramen ovale, 2. Bubble transit through PFO, 3. Follow-up TEE showing the Sideris Buttoned Occluder, 4. Complete closure documented by bubble test.

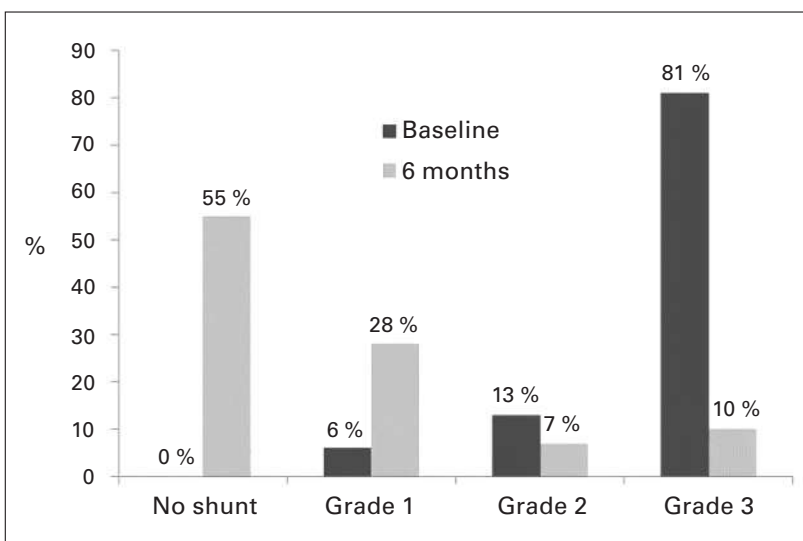


Figure 3: PFO-mediated interatrial shunt at baseline and 6 months after percutaneous closure of patent foramen ovale, as assessed by contrast transoesophageal echocardiography.

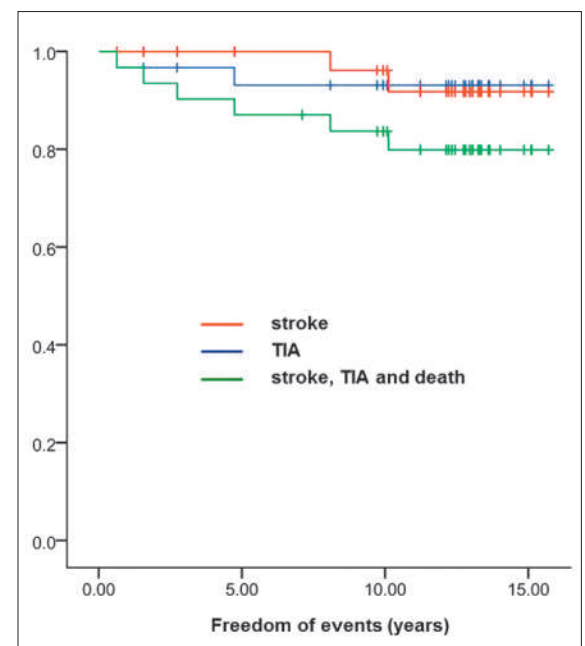


Figure 4: Freedom from recurrent stroke (solid red line), TIA (blue line), and the combined end point of death, ischaemic stroke, TIA, or peripheral embolism (green line) after percutaneous closure of patent foramen ovale using the Sideris Buttoned Occluder.

the TIAs occurred despite therapeutic oral anticoagulation in a 68-year-old patient who developed atrial fibrillation 4 years after PFO closure. There were no relevant bleeding complications. Survival free from recurrent ischaemic stroke, TIA, or peripheral embolism was 97% at 1 year, 90% at 5 years, and 84% at 10 years (fig. 4).

Two patients (with a 33 and 20 mm SBO in place, respectively) underwent implantation of a second PFO occluder device (second devices one SBO 25 mm and one SBO 15 mm) owing to a significant residual shunt, in one case after having suffered a recurrent peripheral embolism. No periprocedural complications occurred during the second intervention. Complete PFO closure was finally achieved in one patient. In the second patient, implantation of a third device (Amplatzer PFO 25 mm) was required and finally resulted in complete PFO occlusion. One patient with a documented residual shunt underwent surgical PFO closure after having suffered a recurrent TIA.

Increasing body mass index (OR 1.6; 95% CI 1–2.6; $p = 0.045$) and smoking history (OR 9.1; 95% CI 0.86–97.3; $p = 0.04$) were both significant predictors of recurrence.

Discussion

We report the late clinical follow-up of a cohort of 32 patients with presumed paradoxical embolism treated at a single centre using the SBO, mainly with regards to the follow-up duration of over 10 years. These data represent the early technical experience in the field of percutaneous PFO closure. The SBO, which was one of the first commercially available devices, has been modified since, but is no longer used at our centre because of the availability of more versatile, effective, and easier to use devices. However, despite the high procedural complication rate of 13%, and the fact that complete PFO closure could be achieved in 55% of cases only, the long-term clinical efficacy of percutaneous PFO closure turned out to be good.

In the literature, the reported success rates of percutaneous PFO closure varies between 90–100%, with complication rates between 0–10%. Complete PFO closure is reported in 51–100% of patients [23], depending on device type and methodology used (transcranial Doppler, transoesophageal or transthoracic echocardiography), and the yearly recurrence rates of ischaemic strokes and transient ischaemic attacks (TIAs) vary between 0–5% [7].

Important differences were observed between the devices used [24–26]. Initial device-related complications inflicted by large delivery systems, device dis-

lodgement and embolisation, structural failure, thrombus formation [27], and inability to reposition or remove the device were reduced by improvements in device design. Anatomical and physiological differences between PFOs and atrial septal defects led to the development of devices specifically designed for percutaneous PFO closure. Current devices for percutaneous PFO closure, such as the Amplatzer PFO Occluder, achieve complete PFO occlusion in >90% of cases with complication rates <1% and yearly recurrence rates <1% [23]. This improvement in device performance is likely to positively impact clinical outcome.

During long-term follow-up of up to 15 years, the risk of stroke or death after transcatheter treatment of PFO with or without associated ASA was <1% per year. The low recurrence rate corresponds with the long-term outcome (mean follow-up of 9.2 ± 3.0 years) previously described by our group [28] and compares favourably with medical treatment [11, 29].

However, the three randomised trials completed so far, CLOSURE (Evaluation of the STARFlex septal closure system in patients with a stroke and/or transient ischaemic attack due to presumed paradoxical embolism through a patent foramen ovale) [12], RESPECT (Randomized evaluation of recurrent stroke comparing PFO closure to established current standard of care treatment) [13], and PC trial (Percutaneous closure of patent foramen ovale and cryptogenic embolism) [14], were negative with regards to their primary endpoints. It is of note that CLOSURE had important methodological weaknesses, particularly the presumably high rate of residual shunt owing to the use of the STARFlex occluder and the short follow-up period (<2 years). Nonetheless, secondary analyses of RESPECT (e.g., per protocol or as treated cohort) demonstrated more favourable outcomes in the closure group. Importantly, several dedicated meta-analyses reported superiority of device closure with the Amplatzer PFO Occluder, enforcing the crucial role of device selection [30, 31]. In the PC trial, obvious overestimation of the recurrence rate at 4 years of follow-up (12 vs 5.2% in the medical group) led to a clear lack of power preventing the study from reaching statistical significance. The long-term outcomes described in our study provided further evidence that recurrent embolic events after percutaneous PFO closure for treatment of cryptogenic embolism are rare.

Conclusions

Despite the high periprocedural complication and residual shunt rates, percutaneous PFO closure using the Sideris Occluder presented no long-term safety

concern. The rate of recurrent events 10 years after percutaneous PFO closure is low.

Limitations

Since both PFO and cryptogenic stroke are prevalent conditions, they may coexist without causal relationship in many patients. Percutaneous PFO closure in patients with falsely PFO-related strokes will not influence recurrent embolic events, a circumstance likely to contribute to the small recurrence rate despite successful PFO closure in our and other series. Nonetheless, these patients will be protected against true paradoxical embolism. It has to be emphasised that the true therapeutic efficacy of percutaneous PFO closure as adjunct or alternative to medical treatment can only be ascertained by randomised studies.

Remark

The abstract of this manuscript was displayed as a poster on 31st August 2010 at the occasion of the European Congress of Cardiology in Stockholm, Sweden, and as such published in *European Heart Journal* (DOI: <http://dx.doi.org/10.1093/eurheartj/ehq289> 589–871; First published online: 28 August 2010).

Disclosure statement

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