Complications and mid-term outcome after percutaneous patent foramen ovale closure in patients with cryptogenic stroke

J.G.L.M. Luermans, M.C. Post, H.W.M. Plokker, J.M. ten Berg, M.J. Suttorp

Background: Percutaneous patent foramen ovale (PFO) closure seems to reduce the risk of recurrent thromboembolism. We report the safety and efficacy of percutaneous PFO closure in our centre.

Methods: All patients, >16 years of age, who underwent a percutaneous PFO closure in our centre were included. Reoccurrence of stroke, transient ischaemic attack (TIA) and peripheral thromboembolism were assessed. Periprocedural and mid-term complications are reported.

Results: Eighty-three consecutive patients (mean age 49 ± 13 years) were included. Indications for PFO closure were cryptogenic stroke (59.0%), TIA (33.7%), peripheral embolism (2.4%) and other (4.8%). For PFO closure, a Cardioseal/Starflex device was used in 63 patients and an Amplatzer PFO occluder device in 20 patients. Stroke recurred in 1.2%, TIA in 3.6%, peripheral embolism in 0% during a mean follow-up of 1.9 ± 1.2 years. Major periprocedural complications occurred in 1.2%. The mid-term complication rate was 2.4% and only consisted of minor complications. During follow-up, a residual right-to-left shunt was present in 5.7% of the patients. No significant difference in outcome, complications or residual shunting could be documented between the two device types.

Conclusion: In our centre, the percutaneous closure of a PFO seems to be a safe and effective procedure to prevent recurrence of paradoxical thromboembolic events. (*Neth Heart J* 2008;16:332-6.)

Keywords: patent foramen ovale, percutaneous closure, cryptogenic stroke, safety

The presence of a patent foramen ovale (PFO) with or without an atrial septal aneurysm (ASA) has been associated with cryptogenic stroke or stroke of undefined cause, especially in young adults.¹⁻³ Paradoxical embolism through a PFO is thought to be the most likely stroke mechanism.^{4,5} Patients with cryptogenic stroke related to PFO, particularly those with an associated ASA, seem to be at risk for stroke recurrence.⁶⁻⁹ High recurrence rates of stroke or transient ischaemic attack (TIA) are reported after medical treatment.^{9,10}

Percutaneous PFO closure is suggested to be an alternative or an additive to medical therapy for secondary prevention of (cryptogenic) stroke. This technique has been shown to be feasible in patients with presumed paradoxical embolism.¹¹⁻¹⁴ Differences in efficacy, safety, and outcome after this procedure, using different types of devices, have been reported.¹¹⁻¹⁶ Most of these studies are limited by a short follow-up period.

In this single-centre study, we report safety and efficacy of percutaneous PFO closure during mid-term follow-up, using two types of closure devices.

Methods

Study population

All patients (>16 years of age) who underwent a percutaneous PFO closure in our centre between May 1998 and November 2006 were included. In all these patients, the PFO was considered to be related to one of the following clinical manifestations: a documented presumed paradoxical thromboembolic event, such as stroke, TIA, or a peripheral embolism or in a few cases decompression illness, pulmonary arterial hypertension with refractory hypoxaemia or the presence of a therapeutically resistant migraine with aura. In case of presumed paradoxical embolism, other sources of systemic emboli were ruled out. The presence of a PFO was confirmed by contrast transoesophageal echocardiography (TEE) with a spontaneous or provokable (Valsalva manoeuvre) right-to-left shunt

J.G.L.M. Luermans

M.C. Post

H.W.M. Plokker

J.M. ten Berg

M.J. Suttorp

Department of Cardiology, St Antonius Hospital, Nieuwegein, the Netherlands

Correspondence to: M.C. Post

Department of Cardiology, St Antonius Hospital, PO Box 2500,

3430 EM Nieuwegein, the Netherlands

E-mail: m.post@antonius.net

(RLS). An atrial septal aneurysm (ASA) was defined as a bulging of the septum of at least 10 mm.

PFO closure

Closure of the PFO was performed under general anaesthesia (propofol) and continuous TEE monitoring. After accessing the right femoral vein, a bolus of 5000 U of heparin was administered. Sheaths up to 12 French were used. The devices were implanted under fluoroscopic and echocardiographic guidance according to the standard technique as previously reported.¹⁴ The choice of the device type was made in accordance to the clinical preference of the interventional cardiologist. All patients received an intravenous prophylactic dose of antibiotics one hour before and six hours after PFO closure (in most cases cefuroxim).

Within 24 hours of closure, a chest X-ray and a transthoracic echocardiogram (TTE) were performed. All patients were discharged on antiplatelet therapy (clopidogrel for at least four weeks and low-dose aspirin for at least six months). Prophylaxis against bacterial endocarditis was advised for a minimum of six months after the closing procedure.

Follow-up evaluation: outcome, complications and efficacy

Follow-up information was obtained by periodical outpatient visits and phone calls. The most recently available medical records were reviewed.

Re-occurrence of stroke, TIA, or any other thromboembolic event were recorded. All neurological embolic events needed to be established by a neurological evaluation and, in case of stroke, confirmed by the appropriate cerebral imaging studies.

All procedural complications immediately related to the closing procedure and occurring within two months were recorded. Mid-term complications occurring at least two months after the closing procedure were retrieved from the most recently available medical records. Complications were divided into major and minor complications according to the classification scheme of Khairy et al.¹⁷ According to this review article, major complications include haemorrhage requiring blood transfusion, occurrence of cardiac tamponade, need for procedure-related surgical intervention, massive fatal pulmonary emboli and death, related to the closing procedure. Minor complications were defined as device malpositioning with successful catheter repositioning, bleeding not requiring blood transfusion, occurrence of new onset atrial arrhythmias (atrial flutter or fibrillation), transient atrioventricular block, device arm fractures, device embolisation with successful catheter retrieval, asymptomatic device thrombosis, need for re-catheterisation, transient air embolism, transient ST-segment elevation, femoral arteriovenous fistula formation, femoral haematoma, and other minor complications related to the closing procedure.

Efficacy of PFO closure was defined as the absence of residual shunting, based on a contrast TTE or TEE study, performed six months after PFO closure.

Statistical analysis

Descriptive statistics were used to report patients' characteristics. Continuous variables were tested on normality and, if present, reported by mean $\pm$ standard deviation (SD). Percentages were used to report categorical variables. Patients data were compared among groups with χ^2 or Fisher's exact test for nominal variables and independent Student's t-test for continuous variables. Kaplan-Meier survival analysis was done on the re-occurrence of stroke, TIA or peripheral embolism. Curves were compared using the log-rank test. All tests were two sided and $p < 0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS software (SPSS Inc., version 11.5 for Windows).

Table 1. Patients and PFO characteristics and indications for PFO closure.

	Number or value	Percentage
Total	83	-
Mean age $\pm$ SD (years)	49.3 $\pm$ 12.9	-
Men	52	62.7
PFO characteristics		
RLS spontaneous	37	44.6
RLS Valsalva	83	100
Aneurysm IAS	29	34.9
Indication for closure		
Stroke	49	59.0
TIA	28	33.7
Peripheral embolism	2	2.4
Decompression illness	1	1.2
PAT with refractory hypoxaemia	2	2.4
Migraine	1	1.2
Closure devices		
Cardioseal/Starflex	64	77.1
- 23 mm	9	10.8
- 28 mm	52	62.7
- 33 mm	3	3.6
Amplatzer PFO occluder	19	22.9
- 9 mm	1	1.2
- 18 mm	2	2.4
- 25 mm	9	10.8
- 35 mm	7	8.4

SD=standard deviation, PFO=patent foramen ovale, RLS=right-to-left shunt, IAS=intra-atrial septum, TIA=transient ischaemic attack, PAT=pulmonary arterial hypertension, mm=millimetres.

Results

Patient and closure characteristics

Between May 1998 and November 2006, percutaneous PFO closure was performed in 83 consecutive patients: 52 men and 31 women, with a mean age of 49.3 ± 12.9 years. Seventy-seven patients (93%) had a history of a cerebral paradoxical embolic event prior to PFO closure. Twenty-two (26.5%) of them had suffered multiple cerebrovascular events. Patient and PFO characteristics and the indications for PFO closure are summarised in table 1.

The devices used for PFO closure were the Cardioseal/Starflex device in 64 (77.1%) and the Amplatzer PFO occluder device in 19 (22.9%) patients.

Follow-up evaluation

Outcome

One patient (1.2%) suffered a stroke, three patients (3.6%) a TIA and none a peripheral embolism, during a mean follow-up of 1.9 ± 1.2 years.

A 58-year-old man developed a stroke 0.4 years after PFO closure with an Amplatzer device. In this patient residual shunting was present. A 61-year-old man and a 57-year-old woman suffered a TIA nine days and 1.1 years after PFO closure with a Cardioseal/Starflex device, respectively. Echocardiography revealed no residual shunting in these patients. Finally, a 61-year-old man developed a TIA 1.0 year after PFO closure with an Amplatzer device, despite no residual shunting at echocardiography.

Kaplan-Meier event-free survival curves for the recurrence of stroke, TIA or peripheral embolism for both devices are plotted in figure 1.

During the follow-up period, a 42-year-old man died 0.2 years after PFO closure due to suicide. Follow-up data are summarised in table 2.

Figure 1. Kaplan-Meier event-free survival for the two types of device used for PFO closure.

Table 2. Outcome, complications and efficacy related to the type of device used for PFO closure.

	Cardioseal/ Starflex	Amplatzer	P
Number, n (%)	64 (77)	19 (23)	
Re-occurrence, n (%)	2 (3)	2 (10)	0.24
- Stroke	0 (0)	1 (5)	0.24
- TIA	2 (3)	1 (5)	0.57
- Other thromboembolic event	0 (0)	0 (0)	-
Death not related to PFO closure, n (%)	1 (2)	0 (0)	1.0
Early complications, n (%)			
- Mal-unfolding of device	1 (2)	0 (0)	1.0
- AV block	0 (0)	1 (5)	0.24
- Inguinal haematoma	1 (2)	0 (0)	1.0
- New atrial arrhythmia	7 (11)	0 (0)	0.19
Mid-term complications, n (%)			
- New atrial arrhythmia	2 (3)	0 (0)	1.0
Atrial arrhythmia total	9 (14)	0 (0)	0.11
Efficacy, n (%)			
- Residual shunting*	2 (4)	2 (15)	0.15

PFO=patent foramen ovale, n=number, TIA=transient ischaemic attack, AV=atrioventricular. *Data available for 70 patients.

Complications

The major complication rate was 1.2%. The total periprocedural complication rate, both major and minor complications, was 12.0%, according to the classification scheme mentioned previously.¹⁷ The only major periprocedural complication occurred in a patient when the Cardioseal/Starflex device did not unfold. While trying to remove this device, it was lost in the subcutis, making a minimal surgical procedure necessary. One month later, this patient successfully received an Amplatzer device. However, he developed a TIA during follow-up; a residual shunt was present. Minor periprocedural complications included the following: one patient developed atrioventricular block shortly after implantation of an Amplatzer device. He was treated with a temporary pacemaker and recovered quickly without atrioventricular conduction abnormalities. One patient suffered an inguinal haematoma, which recovered spontaneously without the need for surgery or blood transfusion. Seven patients suffered atrial arrhythmias, mostly atrial fibrillation, within two months of PFO closure with a Cardioseal/Starflex device. They were all treated medically, resulting in sinus rhythm.

The mid-term complication rate was 2.4% and consisted of only minor complications. These included two patients who developed atrial fibrillation after PFO closure using a Cardioseal/Starflex device. They both required medical treatment and are doing well.

None of the patients with atrial arrhythmias developed a recurrent thromboembolic event. All these data are summarised in table 2.

Efficacy

TTE for diagnosing residual shunting could be obtained in 70 patients (84%). Six of them underwent additional TEE, because of an inconclusive TTE. Within a mean follow-up time of 0.6 years, residual shunting was present in four patients (5.7%). Stroke recurred in one of these four patients. There was no statistical difference in the occurrence of a residual shunt between the devices ($p=0.15$). These data are summarised in table 2.

Discussion

The main finding of this study is that percutaneous PFO closure in patients with a history of paradoxical embolic events appears to be safe and effective with a low recurrence rate of cerebral ischaemia, independent of the type of device used for closure.

Recurrence of thromboembolic events

Patients with cryptogenic strokes related to a PFO are at risk for stroke recurrence.⁶⁻⁹ Percutaneous PFO closure has been shown to be effective in the prevention of recurrent thromboembolic events.^{11,12,14,15,18,19} Although randomised trials that compare medical treatment and transcatheter closure are lacking, the case-control study by Windecker et al. showed that percutaneous closure related to the presence of a PFO, in cryptogenic stroke patients, was at least as effective as medical treatment for prevention of recurrent cerebrovascular events and even more effective in patients with complete PFO closure and a history of more than one cerebrovascular event.²⁰ Additionally, Khairy et al. reported a one-year rate of recurrent neurological thromboembolism of 0 to 4.9% with transcatheter intervention as compared with 3.8 to 12.0% with medical treatment.¹⁷

We found a yearly recurrence rate of thromboembolic events of 2.5%. These results are comparable with previous reports. All events occurred in the first year following PFO closure. Indeed, Windecker et al. reported that the recurrence rate of thromboembolism seemed to be highest in the first year after PFO closure, as hypothesised to be due to device-related problems.¹⁴ However, a recurrent neurological event might not be related to failure of the PFO device (residual RLS, thrombus formation on the device) alone. We only found residual shunting in one patient with a recurrence of stroke. The events that occurred in the other patients might be due to atherosclerosis instead of device failure. Indeed, all patients who had a recurrence of stroke or

TIA were older than 55 years and at this age the relationship between the presence of a PFO and cryptogenic stroke is less well defined.^{1,21,22}

Moreover, the prevalence of ASA of 34.9% that we found in our study population appeared to be higher than most previous studies.^{11,14,15,19} Mas et al. indicated that cryptogenic stroke patients with both PFO and ASA carry an increased risk of stroke recurrence when treated medically.⁹ No such association has been reported after PFO closure. Nevertheless, our study population might constitute patients at high risk for stroke recurrence.

Complications

A systematic review by Khairy et al., in which periprocedural complications of ten transcatheter PFO closure studies were divided into minor and major, showed a complication rate of 7.9 and 1.5%, respectively.¹⁷ Braun et al. reported a peri-interventional complication rate of 3% and a complication rate of 1.6% for a median follow-up time of 24 months. Their study included 307 consecutive patients undergoing PFO closure, using three different types of devices.¹¹ Post et al. found a periprocedural complication rate of 7.1% and a mid-term complication rate of 1.8% after percutaneous PFO closure in 112 patients without differences between several types of devices. However, the overall major complication rate was low, 1.8%.¹²

The results of our study are concordant with those previously reported in the literature. A periprocedural complication rate of 12% was found, of which only 1.2% were defined as major. Transient atrial fibrillation was responsible for most of these complications (8.4%). The mid-term complication rate was 2.4% and consisted of atrial arrhythmias only. We found no statistical differences in the complication rate between the two devices used for PFO closure. These results indicate that percutaneous PFO closure in our centre can be considered to be safe.

Efficacy

Reports about residual shunting after PFO closure are conflicting and range from 4 to 49%, probably dependent on the use of different types of devices, the follow-up time and the method used for diagnosing residual shunting.^{11,12,14,15,18,19,23} Windecker et al. found residual shunting in 27% of 80 patients using TEE with contrast six months after PFO closure. The presence of a residual shunt was a predictor of recurrent thromboembolic events with a relative risk of 4.2.¹⁴ However, Martin et al. showed a progressive increase in the number of patients without a residual shunt during the first year of follow-up using TTE with contrast. Full occlusion was present in 51% of the 110 patients at six months follow-up and in 66% at 12 months follow-up using two types of devices: the buttoned device or CardioSEAL Occluder device.¹⁵ However, Schwerzmann et al. reported a significant difference in the prevalence of a residual shunt diag-

nosed by TEE with contrast between the Amplatzer PFO Occluder and the older PFO STAR device. Six months after PFO closure complete closure was found in 94% of 50 patients in whom the PFO was closed with the Amplatzer PFO Occluder and 66% complete closure was found in a similar number of patients in whom an older (first) generation PFO STAR device was used.¹⁶ However, others found residual shunting in 10.8% of 403 patients six months after PFO closure using the three generations of PFO STAR devices.²⁴

We found a prevalence of residual shunting of 5.7% six months after PFO closure, with no significant difference between the two device types. These results appear to be better than previously reported data. An explanation for this could be that we generally used a contrast-TTE examination to diagnose residual shunting as compared with contrast-TEE in most previous studies, which is the gold standard. A TTE could give an overestimation or underestimation of residual shunting.²⁵

Limitations

The first limitation is the relatively small patient population, which limits comparison of the re-occurrence of paradoxical embolism between the two devices used. However, this is due to the single-centre character of the study. Secondly, we generally used a contrast-TTE as the imaging technique to detect residual shunting. Both overestimation and underestimation of a right-to-left shunt compared with TEE are possible with this technique.²⁵

Conclusion

In our centre, we found that percutaneous closure of a PFO, which is suggested to be related to a paradoxical embolism, is a safe and effective procedure to prevent the recurrence of paradoxical thromboembolic events, independent of the device used for closure. ■

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