

Occlusion of PFO with a dedicated adjustable device: influence on one year outcome

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KEYWORDS

Patent foramen ovale, transcatheter closure of PFO, residual shunt, dedicated PFO closure system

Abstract

Aims: Though the association of patent foramen ovale with cryptogenic stroke in young patients has been known for 20 years, most interventional closure systems are not specifically designed for PFO closure, but instead are adapted from ASD closure systems. We describe the safety, feasibility and efficacy of transcatheter closure of PFO using a dedicated adjustable device specifically designed to overcome some of the pitfalls of PFO occlusion like erosion, left atrial thrombus formation, embolisation, maladaptation to cardiac structures and excessive foreign material deposition.

Methods and results: Seventy-two consecutive patients, aged between 20 and 72 years, underwent PFO occlusion using the Premere[®] PFO occluder, for the greater part for presumed paradoxical embolism causing cryptogenic stroke or transient ischaemic attack. Forty patients received the 20 mm, while 32 received the 25 mm device. Implantation was successful in all patients. Residual shunt rate, excluding absolutely trivial shunts, was 2.8% at six months on contrast TEE study. Peri- and postprocedural adverse events with some possibility of a causal link to the procedure occurred in six patients. The postprocedural annual recurrence rate (0.99%) was lower than reported in most other series.

Conclusions: PFO occlusion using the dedicated Premere[®] PFO occluder is effective and safe. The residual shunt rate and post-interventional recurrence rate compares favourably to the literature.

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Introduction

The association of a patent foramen ovale (PFO) with cryptogenic stroke in young patients (who show a three to fourfold PFO prevalence) has been recognised for over twenty years^{1,2}. Since this time, anatomic and pathophysiological features have been described that have a predisposition to morbidity in patients with patent foramen ovale, amongst them atrial septal aneurysm³, large PFO size⁴, prominent Eustachian valve⁵ and a thrombogenic state^{6,7}. While active research for PFO associated diseases during these 20 years has pointed to a number of morbidities that have, more or less, been conclusively shown to be associated with PFO, for most of them a scientific proof of benefit by randomised studies is still awaited, though outcomes in individual cases are very intriguing and highly suggestive of a major benefit of PFO closure in various pathologies.

The answer to the question of whether or not the intervention favourably influences the natural course of PFO associated disease mainly depends on two factors: the likelihood that the association is a causal relationship; and the probability that the intervention has a considerably lower short- and long-term complication rate as compared to the natural course of disease. Thus, the type of device used might be of particular importance to outcome.

While in the early days interventional closure systems were used that were not specifically designed for PFO closure, more specific PFO closure systems have since been developed.

This article describes our experiences with a new device⁸ that is specifically designed to overcome some of the pitfalls of PFO occlusion like erosion, left atrial thrombus formation, device embolisation, maladaptation to the cardiac structures and excessive foreign material deposition.

Methods

A thorough diagnostic work-up of each patient was accomplished with the aim of establishing a reasonable likelihood of presumed paradoxical embolism, including:

- neurologic evaluation with MRI brain imaging (with MR angiogram)
- Doppler sonography of the cerebral circulation (with search for high intensity signals on transcranial Doppler),
- detailed cardiac investigation including transthoracic and transesophageal echocardiogram,
- 24 hour Holter monitoring for exclusion of atrial fibrillation,
- coronary angiography to detect coronary disease and to facilitate judgement as to presence of generalised atherosclerosis,

If the presence of PFO was still considered to have played an important part in the patient's pathology after this exam, PFO occlusion was performed as previously described¹⁰.

Patients with a PFO stretch size above 16 mm were excluded and treated with another device, as were patients with a large ASA and stretch size >12 mm. Patients were pretreated with 5000 units of heparin and a loading dose of 300 mg aspirin, the latter being continued at a daily dose of 100 mg for six months. The procedure was performed under dual imaging by standard fluoroscopy, as well as transesophageal echocardiography. Great care was taken to

optimally place the device with the clamps lying flat on the septum, to avoid any persistent shunting on colour flow imaging or on contrast imaging with Valsalva as deemed clinically appropriate. All patients received prophylactic antibiotics in one to three doses within 24 hours of the intervention.

Postoperative follow-up included visits at one, three, six and 12 months and yearly thereafter, with TEE at three or six months or quarterly until residual shunts were closed. In nine patients, follow-up was incomplete in terms of TEE, all of them being free of residual shunts on TTE and without recurrences.

The study was conducted in accordance with the declaration of Helsinki and was approved by the local ethics committee.

Results

Between February 2004 and June 2008, 72 consecutive patients referred for occlusion of patent foramen ovale underwent PFO occlusion using the Premere® PFO occluder (St. Jude Medical Europe, Zaventem, Belgium). Median follow-up was 12 months.

Patients were equally distributed in sex (males=37, females=35 patients), mean age was 47.2±10.8 years. The reasons for referral included presumed paradoxical cerebral embolism in 65 patients (42 strokes, 25 TIAs), presumed paradoxical myocardial infarction (n=5) and various other disorders in addition to these such as migraine (n=7), peripheral arterial embolism (n=2), tinnitus (n=5). PFO occlusion was performed in one patient for prophylactic reasons only, this patient coming from a family in which several members had suffered stroke due to paradoxical embolism. Fifty-seven patients had one, and 14 patients had two or more previous presumed paradoxical embolic events.

Thrombophilia screening was done in all patients and revealed some sort of thrombophilia in 12 patients (17%). Patients with significant atherosclerosis were excluded, however, in 16 patients non-significant plaques in carotid arteries were found, but were judged not to have contributed to the cerebrovascular accidents. Diabetes was present in six patients, hypertension in 22 and hyperlipidaemia in 17 patients.

Echocardiographic imaging revealed PFO in 55 patients, slight left to right shunting on colour Doppler imaging with PFO morphology ("PFO like ASD") in 17 patients. Atrial septal aneurysm was found in nine patients (ASA defined as septal shift > 15 mm). All patients had sizing of the PFO with an AGA Medical (AGA Medical Corp., Minneapolis, MN, USA) or a NMT (NMT Medical Inc., Boston, MA, USA) sizing balloon, which revealed an average PFO stretch size of 9±4 mm. Median fluoroscopy time including diagnostic left and right heart catheterisation in 66/72 cases was 10.7 min and median x-ray dose area product was 24.8 Gray x cm².

The 20 mm Premere® device was used in 40 patients (mean stretch size 7.7 mm; range 4, up to 12 mm), while in 32 patients the 25 mm device was preferred (mean stretch size 10.8 mm, range 5 up to 16 mm, predominantly used in patients with ASA or with hypertrophic lipomatous septum).

Procedural adverse events included atrioventricular nodal re-entry tachycardia in two patients, aneurysm formation in the groin in one case, and transient ST elevations in one case, probably due to small air embolism (complete resolution, no enzyme rise).

Postprocedural adverse events included early transient atrial fibrillation (n=1), atrial flutter (n=1) and right atrial thrombus formation (n=1; thrombus diameter 5 mm, found three months after implantation on TEE, not adherent to the device, in a patient with thrombophilia). There was one recurrent stroke without long-term neurologic deficits in a patient with pre-existing arteriosclerosis (annual recurrence rate 0.99%), two patients with visual disturbances not distinguishable from migraine aura and one patient with intense headaches for a few days in the early post-intervention phase. There was one patient having a focal and a secondarily generalised focal seizure due to her pre-intervention brain infarction, one peripheral arterial hypoperfusion in a patient with peripheral arterial disease and one patient developed cerebral basal ganglia bleeding four months after intervention, clearly shown not to be associated with ischaemia. Sixty-one patients, N=61/72 (85 %), were free of any postprocedural adverse events, and in six there was some likelihood of causal connection to the procedure or postoperative drug therapy, three of these representing possible migraine equivalents.

Residual shunt rate was 7/72 (9,7%) at six months on contrast TEE Valsalva study, however, shunts were absolutely trivial in all but two of them.

Discussion

In the last 20 years of active research into PFO associated diseases, a number of morbidities have been more or less conclusively shown to be associated with PFO:

- cryptogenic stroke and transitory ischaemic attacks (TIAs)
- peripheral arterial embolism
- decompression illness in both divers and pilots
- stroke/ TIA associated with pulmonary embolism and/or prothrombotic states
- myocardial infarction with normal coronary arteries
- platypnea-orthodeoxia syndrome
- migraine with aura (especially in individuals with history of cryptogenic stroke/TIA)
- hypoxia in sleep apnoea, COPD and bronchial asthma or after LVAD implantation
- ischaemic colitis
- recurrent brain abscess
- transitory global amnesia
- left heart valvular disease in carcinoid syndrome

Though for most associated morbidities scientific proof of benefit by randomised studies has not yet been done, outcomes in individual cases are very intriguing and highly suggestive of a major benefit of PFO closure in various pathologies.

Whether or not the intervention favourably influences the natural course of PFO associated disease again mainly depends on two factors:

- the likelihood that the association represents a causal relationship
- the probability that the intervention has a considerably lower short and long term complication rate as compared to the natural course of disease.

The list of potential adverse events after PFO closure comprises device embolisation (0.5-1.0 %), thrombotic debris on the device

(0.4-0.6%), thromboembolism and recurrences (0-4.9%) particularly found in patients with residual shunts, atrial fibrillation (2-4% in the first few weeks; may be unrelated to closure and rather due to first diagnosis of a pre-existing condition), perforation/erosion with pericardial tamponade (0-0.5%), pulmonary embolism (more likely in individuals with co-existing thrombophilia), air embolism, atrioventricular block, retroperitoneal bleeding, sudden death, retropharyngeal haematoma (intubation trauma), compromise of AV valves, partial obstruction of superior vena cava, haemolysis, silent cerebral microemboli and others.

While in the early 1990s interventional closure systems not specifically designed, developed or adapted for PFO closure were used, specific PFO closure systems have been developed, tested and evaluated within the last ten years, using very different technologies and implantation techniques. The spectrum covers umbrella devices, radiofrequency application and suture techniques, and ranges from systems with relatively large amounts of bulky foreign material to minimised, very soft and thin systems and biodegradable devices.

This report describes the first 72 procedures we accomplished with a recently developed device⁸, that is specifically designed to overcome some of the pitfalls of PFO occlusion discussed above such as erosion, left atrial thrombus formation, device embolisation, maladaptation to the cardiac structures and excessive foreign material deposition. To achieve these goals the left atrial disc has been replaced by four nitinol clamps, that are connected to the right atrial disc (a polyester membrane, stretched out by four identical clamps) by a firm string. The distance between the left atrial clamps and the right atrial disk is determined by a stopper on the string, that can be advanced, but does not retract. The device is retractable even after final placement, because it is connected to the string, by which it can be retrieved even after implantation. Thus the device has little foreign material, a variable distance between left and right device parts to allow adjustment to anatomy, is very flexible, has an exceedingly low risk of device embolisation and at least, in the left atrium, is of low thrombogenicity, since no thrombogenic material is left there.

The PFO device used in this moderate size group of patients proved to be effective and safe. In 90.3% of patients complete occlusion as confirmed by TEE was achieved at six months. Post-intervention annual recurrence rate (0.99%) was lower than in most reports in the literature, though it was higher than in our own series of patients in whom atherosclerosis was excluded as thoroughly as possible (0,32%)^{10,11}; natural history of the disease would predict 25% recurrences within four years (6.25% annually)¹². Thus, both procedural outcome and long-term performance of the Premere® device were favourable.

While it has been proposed to occlude PFOs without intraprocedural transesophageal and intracardiac echocardiography¹³, this imaging technique, in addition to x-ray, seemed to be beneficial in this series, since adaptation of the device often led to several readjustments of position.

Recurrence rate has been linked to residual shunt rate and is at least 3-fold increased in patients with residual shunts¹⁴⁻¹⁸. Both the adjustable device design and the diligent application procedure

might have contributed to the low residual shunt rate in this series of only 2.8% (excluding absolutely trivial shunts) at six months, which compares favourably to the 10% shunt rate with the AGA Medical Device reported by Wahl¹⁴.

We did not use clopidogrel or heparin for post-interventional treatment, and treated all patients with 100 mg aspirin for six months, as it had been our routine procedure with other devices before¹⁰. However, in devices with higher thrombogenicity, it might be reasonable to more aggressively use platelet inhibition or anticoagulation for a limited time period.

This study has several limitations. Since it was not a random application of devices it does not prove superiority of the device used. Nevertheless, it shows that very good results can be achieved when the Premere® device is used properly. Secondly, the event rate is small, but systematic screening for silent paradoxical embolism has not been performed. However, the very low residual shunt rate makes a higher rate of recurrent events unlikely. The occurrence of a right atrial thrombus, possibly attached to the device, in a series of less than 100 patients is of some concern, however, our series had an unusual high rate of thrombophilia with 17% of the patients. The fact that the thrombus was seen only on the right atrial side speaks in favour of the assumption that thrombogenicity is lower in designs with metal clamps only, like the left atrial part of the Premere® device.

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