

Current Management of Patients with Patent Foramen Ovale and Cryptogenic Stroke: Our Experience and Review of the Literature

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ABSTRACT

Background: Patent Foramen Ovale (PFO) occurs in approximately 25% of the population and has been implicated in the etiology of cryptogenic stroke. Although the exact mechanism of PFO's role in stroke has not been defined, there is a growing body of evidence that supports both the safety and therapeutic benefit of PFO closure in cryptogenic stroke. Current methods of therapy include anticoagulation, surgical closure, and percutaneous closure.

Methods: We completed a retrospective analysis of data from the first 20 PFO closures at our institution and evaluated the current literature on PFO treatment.

Results: Percutaneous closure had a 100% technical success rate. There were no procedural complications and only 1 episode of supraventricular arrhythmia requiring therapy.

Conclusion: Percutaneous closure is associated with a high technical success rate, decreased morbidity compared to surgery, and equal benefits after endothelialization of the device. As the mechanisms involved in PFO are better delineated, clear guidelines can be established for the percutaneous closure and follow-up of PFO.

INTRODUCTION

Stroke is one of the leading causes of serious mortality and long-term disability in the United States, killing an estimated 167,661 people in 2000 alone. Each year about 700,000 people experience a new or recurrent stroke.¹ In approximately 40% of these events, an eti-

ology cannot be determined, and these are referred to as cryptogenic strokes.^{2,3} Patent foramen ovale (PFO) (Figure 1) has become increasingly implicated as a risk factor for cryptogenic stroke,⁴ and optimal management of these patients remains controversial. Traditional medical therapy for these patients has involved either anticoagulation with warfarin or antiplatelet therapy with aspirin, however, medical therapy has been associated with an average annual recurrence rate of 3.8%.² Surgical closure, although associated with 0% stroke recurrence rate in small case studies, is associated with major surgical morbidity.⁵⁻⁷ Recently, percutaneous closure of PFO has been proposed as a less invasive alternative to treat these patients. The aim of this paper is to define the scope of the problem, report our experience with percutaneous closure of PFO, and review the literature about the current management of these patients.

BACKGROUND

Cryptogenic stroke accounts for 30%-40% of all strokes.³ PFO has been reported to occur in approximately 46% of cryptogenic stroke patients and only 11% of matched controls.⁸ Of the 700,000 strokes suffered each year in the United States, 75% of these are ischemic, of which approximately 30% (or 160,000) are cryptogenic strokes. By extrapolation, 70,000 of these cryptogenic strokes may be associated with PFO and may benefit from device closure of these defects. When one considers other medical complications associated with PFO, such as paradoxical peripheral emboli, decompression illness, and migraine with aura, the number of patients who may benefit from PFO closure each year in the United States is even larger.

During fetal development, the foramen ovale, formed by a space between the septum secundum and the septum primum, allows blood to pass from the right to the left (from the umbilical vein to the fetal arterial circulation) without passing through the lungs. After birth, increased left-sided pressures in concur-

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rence with decreased right-sided pressure presses the septum primum (from the left) across the septum secundum (arising from the right). In time the two membranes fuse. Failure of the membranes to fuse can occur in about a fourth of the population.³ In this group, the foramen ovale remains patent, thereby allowing communication between the right and left atria. In theory, increased right-sided pressures can result in a right to left shunt and subsequent paradoxical emboli. The prevalence of PFO appears to decline with age, however, this may be secondary to a greater incidence of mortality among patients with PFO.⁹ An atrial septal aneurysm (ASA), usually a floppy septum primum, has been implicated as an increased risk factor for recurrent stroke.¹⁰ Although the overall prevalence of ASA as an isolated abnormality is low, it is common in association with PFO.

Other clinical problems, such as migraine headaches, decompression illness in divers, and platypnea orthodeoxia have all been associated with PFO, but the exact correlation is poorly defined. In a retrospective analysis by Wilmhurst et al, 40 patients that underwent transcatheter closure of PFOs or atrial septal defect (to resume diving after decompression illness in 29 patients) were interviewed to determine the incidence of migraine headache. Twenty-one patients reported a history of migraine headaches with and without aura prior to closure of an atrial defect. Of the 21 patients, 18 reported either complete cure or improvement of their migraine headaches. Dider et al showed that migraine was not only more frequent in young patients with ischemic stroke and PFO, but that migraine was an independent predictive factor of recurrence in ischemic stroke due to PFO.¹¹⁻¹³ Further investigation regarding a causal relationship is needed.

Since cryptogenic stroke is a diagnosis of exclusion, it is critical that all stroke patients have an appropriate workup prior to being labeled as cryptogenic. The routine work-up involves blood tests evaluating coagulation (protein S, protein C, antithrombin III and antiphospholipid antibody, lupus anticoagulant, factor V Leiden). Other studies include a 12-lead EKG, 24-48 hour EKG monitoring to rule out arrhythmia, echocardiography (preferably transesophageal echocardiography [TEE] for better resolution, and evaluation of the proximal aorta for possible free moving atheroma), carotid ultrasound, and a vascular study such as catheter angiography or magnetic resonance angiography (MRA). Diagnosis of PFO can easily be made by TEE. Evaluation of PFO by TEE can be enhanced further by use of an aerated colloid solution (bubble

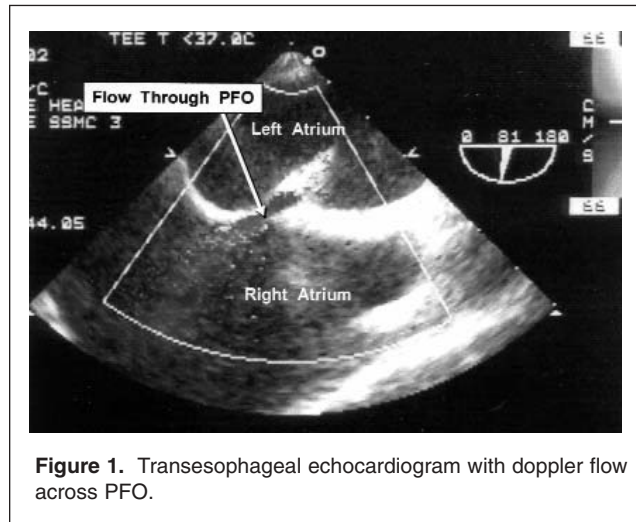


Figure 1. Transesophageal echocardiogram with doppler flow across PFO.

study) at the end of a sustained Valsalva maneuver. Transcranial Doppler is also a sensitive and specific test for PFO.

The management of PFO to date has revolved around 3 treatment options: medical treatment with anticoagulation or antiplatelet therapy, surgical closure, and percutaneous closure. Medical therapy involves anticoagulation or antiplatelet therapy with either warfarin, aspirin, or clopidogrel in combination or alone. In light of major bleeding complications, anticoagulation is a problem when considering the life expectancy of young patients. The WARSS (Warfarin-Aspirin Recurrent Stroke Study Group) study found no difference in the recurrence of ischemic stroke in patients treated with aspirin or warfarin over a 2-year period. However, the 2-year probability of a recurrent event (recurrent ischemic stroke or death) was 16%-18% despite therapy with either agent.¹⁴

Surgical closure in a number of small studies has shown encouraging results. Devuyst et al demonstrated both safety and 2-year event-free follow-up in a study of 30 patients believed to be at high risk for recurrence.⁷ This procedure, however, involves sternotomy with direct closure of the PFO under cardiopulmonary bypass. Cujec et al evaluated medical therapy (warfarin or aspirin), versus no therapy, versus surgical closure in 90 patients. There was a 12% event recurrence rate/patient/year in patients with PFO prior to surgical closure and 5% event recurrence/patient/year among controls. Fourteen patients with PFO underwent surgical repair and there were no recurrences in this group over a 43-month follow-up.⁶ Homma et al reported 4 neurologic events in a 19-month follow-up of 28 patients who underwent surgical closure of PFO. Dearani et al reported 8 transient ischemic accidents (TIAs) in a 2-year fol-

Table 1. Demographics of Patients Undergoing PFO Closure

Clinical Characteristics	N (%)
Sex, male/female	13/7 (65/35)
Diabetes Mellitus	4 (20)
Hyperlipidemia	6 (30)
Hypertension	9 (45)
Smoking	3 (15)
Coronary Artery Disease	6 (30)
Age, mean/(range)	57.5±15 /(31-83)

low-up of 91 patients.⁵ Compared to data on medical therapy alone,⁴ these small case studies of PFO closure appear to show a benefit. Surgical closure, however, is often not a popular option with young patients as sternotomy and the scar it will leave is unappealing to them. Cardiopulmonary bypass also carries a measurable risk and has been associated with decreased post surgical aptitude scores.¹⁵

Percutaneous atrial septal defect (ASD) repair was first performed in 1974,¹⁶ and since that time there have been numerous devices that have been used for percutaneous closure of both atrial septal defects and PFOs. Earlier transcatheter closure of PFO was met with skepticism as device complications and residual shunting lead to a higher recurrence of events. Bridges et al reported 4 TIAs in an 8.4 month follow-up period after percutaneous closure.¹⁷ Improvement in closure devices has resulted in a much higher success rate. Technical problems are rare and include inability to cannulate the PFO, symptomatic air embolism, problems at the site of percutaneous cannulation, ineffective seating of the device, migration of the device, intraprocedural stroke, retroperitoneal hematoma, pericardial tamponade, supraventricular tachycardia, and atrial fibrillation. Martin et al reported a 100% procedural success rate in a series of 110 patients.¹⁸ In their study there were 6 in-hospital adverse events (none of which included stroke or death). Only 1 patient required emergent surgery for device removal and PFO closure. A small or no residual shunt was found in all patients at 24 hours. At 1-year follow-up all but 1 patient had a small or no residual shunt present. Neurologic event recurrence rates approached that of medical therapy in the first year, but then decreased in subsequent years. Meier et al reported complete closure at follow-up in 90%-95% of all patients.⁸ Windecker et al reported a 98% procedural success rate in 80 patients undergoing closure. There were 8 recurrent events (6 TIAs and 2 peripheral emboli) during a mean follow-up of 1.6 years (range 0.1-5.0 years). The

highest risk of recurrence was in the first year following closure with no events occurring after 2 years.¹⁹

Post-closure therapy includes use of an antiplatelet agent (clopidogrel or aspirin) with or without warfarin therapy. Antibiotics are given during the procedure and prophylactically as endocarditis precaution for 6 months post procedure. Eventually the device is completely enclosed with tissue and prophylaxis can stop. A follow-up TEE to evaluate the seating of the device and to assess for residual shunt marks the end of medical therapy.

OUR EXPERIENCE

From August 2002 to June 2003, 20 patients underwent percutaneous closure of PFO at Aurora Sinai and St. Luke's Medical Centers. Nineteen patients underwent closure because of cerebrovascular events and 1 patient suffered a paradoxical embolus to the kidney. All patients underwent thorough preoperative evaluation to rule out alternate sources of emboli. The author's approach to workup included a TEE with bubble study, brain magnetic resonance imaging (MRI), hypercoagulation labs (Prothrombin G20210A, Protein C,S, Antithrombin III, Factor V Leiden, Lupus Anticoagulant, Anticardiolipin antibodies), and a cerebral vascular study (MRA, carotid/cerebral angiogram, or carotid duplex study with transcranial doppler) prior to PFO closure. Lower extremity doppler studies were not available on all patients. Demographic characteristics of these patients are shown in Table 1.

Procedural Overview

The procedure was performed under general anesthesia in 18 patients and with conscious sedation in the remaining 2. All patients received endocarditis prophylaxis prior to implantation and for 24 hours after implantation of the device. Femoral venous access was obtained using a modified Seldinger technique. The PFO was then crossed using a 6Fr. multipurpose catheter under fluoroscopic and TEE guidance. The PFO was then sized using an NMT medical (NMT Medical, Inc.) sizing balloon. The CardioSEAL Septal Occluder® (Figure 2) implant (NMT Medical, Inc.) was prepared and loaded using the standard technique previously described (NMT Medical, Inc. Procedural Overview) and then deployed under TEE and fluoroscopic guidance. At the end of the procedure a bubble study was repeated to look for any residual shunts. Patients were then admitted for overnight observation. All patients underwent a chest x-ray, EKG, and a 2-dimensional echocardiogram prior to hospital discharge. Patient follow-up included a 2-dimensional echocardiogram at 1 month, 3 months, 6 months, and annually thereafter. All patients were discharged on aspirin and

clopidogrel unless arrhythmia or history of DVT necessitated continued warfarin therapy. All patients received American Heart Association (AHA) guideline therapy for endocarditis prophylaxis for 6 months.

Procedural Results

In all but one case, the CardioSEAL Septal Occluder® (NMT Medical, Inc.) was used (Figure 3). The AM-PLATZER PFO Occluder® (AGA Medical Corporation) device was used in 1 patient. Technical success was achieved in 100% of the patients. The majority of the patients received a 28-mm CardioSEAL Septal Occluder® device (n=12). The 33-mm device was used in 3 patients and a 23-mm device in 4 patients. None of the patients experienced any major complications such as perforation, cardiac tamponade, vascular complications, stroke, or MI. Two patients experienced transient ST-segment elevations, which was due most likely to air embolism; however, no wall motion abnormalities were noted on TEE. There was no incidence of device embolization or malpositioning. Length of hospital stay was less than 24 hours in 19 patients.

Follow-up

At a mean follow-up of 8 months none of the patients had a stroke or paradoxical embolism. There were no incidents of endocarditis or thrombus formation on the devices. Two patients experienced paroxysmal atrial fibrillation. One patient required beta-blockers for 2 months to control his atrial fibrillation and has now been in normal sinus rhythm without medication for 8 months. The second patient required antiarrhythmic therapy with amiodarone to control symptoms. No arrhythmias occurred during the procedure.

CONCLUSION

Patent foramen ovale is a common congenital abnormality that affects 25% of the population. Its association with cryptogenic embolism and other paraembolic phenomenon has led to a need for definitive therapy. Unfortunately, no clinical trials comparing the 3 current modes of therapy have been performed in a randomized manner. However, in studies of selected patients there appears to be a clear benefit of PFO closure over medical therapy. The long-term risks of bleeding complications can also be eliminated. Percutaneous closure is a simple procedure requiring only overnight observation. It has replaced the need for surgical closure in all but a few rare cases. As the data linking PFO to other clinical problems continues to grow, so will the indication for percutaneous closure, especially if controlled trials continue to prove its efficacy in alleviating recurrent events.

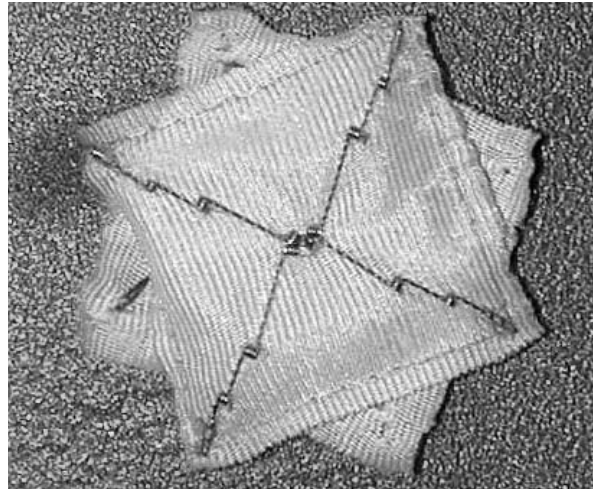


Figure 2. CardioSEAL® Device (NMT Medical).

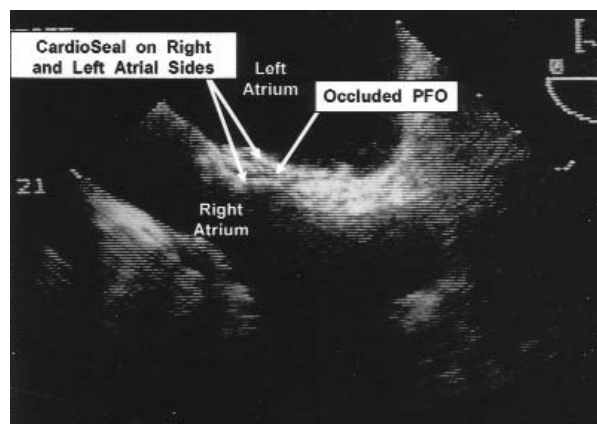


Figure 3. Transesophageal echocardiogram of CardioSEAL® device in place.

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