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# Transcatheter Occlusion of Atrial Septal Defects for Prevention of Recurrence of Paradoxical Embolism

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## 1. Introduction

Stroke is the third most common cause of death in the United States. Stroke also results in substantial health-care expenditures with an estimated lifetime cost from an ischemic stroke of \$140,000 per patient (Rosamond K, 2007). Each year, approximately 795,000 people experience a new or recurrent stroke, of which an estimated 610,000 are first attacks. Mortality data from 2006 indicates stroke accounted for approximately 1 of every 18 deaths in the United States. On average, every 40 seconds, someone in the United States has a stroke (Heart Disease and Stroke Statistics, AHA 2009).

Cryptogenic infarction has had a predominant status among the causes of ischemic strokes, originally demonstrated in the Stroke Data Bank. Sacco and Mohr reported a 40% incidence of cryptogenic stroke in their population (Sacco, Ellenberg, Mohr et al., 1989). A cryptogenic infarction does not have a defined cause despite a complete work-up. It differs from infarction of undetermined causes, which may involve overlapping causes or an incomplete investigation.

Numerous studies have established a higher prevalence of patent foramen ovale (PFO) or atrial septal defect (ASD) in patients with cryptogenic stroke when compared to patients with stroke of determined cause despite correction for recognized stroke risk factors. This relationship has perpetuated the paradoxical embolism theory as a likely stroke mechanism in this patient population (Lechat 1988, Webster 1988, DeBelder 1992, DiTullio 1992).

Emboli leading to stroke can originate either in the systemic arterial circulation or in the systemic venous circulation (paradoxical embolism). A paradoxical embolus originates in the systemic venous circulation and enters the systemic arterial circulation through a PFO, ASD, ventricular septal defect (VSD), or extracardiac communication such as a pulmonary arteriovenous malformation (AVM).

Therapeutic measures for secondary prevention in this patient population can encompass medical treatment or surgical/percutaneous closure of the patent foramen ovale or atrial septal defect as well as coil embolization of pulmonary arteriovenous malformations.

Ongoing randomized clinical studies aim at comparing medical treatment versus closure of atrial septal defects to determine the most effective treatment strategy in this patient population (RESPECT PFO trial, CLOSURE I trial, Gore REDUCE Clinical Study "HLX 06-03).

### **Embryology of atrial septal defects**

#### **Patent Foramen Ovale**

The foramen ovale is a pivotal feature during intrauterine life. The interatrial communication is necessary for the shunting of oxygenated blood from right atrium to left atrium. Beginning at four weeks of pregnancy the primordial atrial septum divides into right and left sides by formation and fusion of two septa: the septum primum and septum secundum. The interatrial septum primum on the left side and interatrial septum secundum on the right side maintain a central opening after having grown from the periphery to the center. This perforation is positioned caudally in the septum secundum and cranially in the septum primum, forming a slit valve that opens when right atrial pressure exceeds the left atrial pressure. The oxygenated blood from the umbilical vein entering through the inferior vena cava from the bottom of the right atrium keeps this window open until after birth.

#### **Postnatal physiologic changes**

At birth, right heart pressure and pulmonary vascular resistance drop as pulmonary arterioles open in reaction to oxygen filling the alveoli. Left atrial pressure may also rise as the amount of the blood returning from the lung increases. Either or both of these mechanisms may cause flap closure against the septum secundum.

This fusion is complete by age two in about 75% of individuals, but persistent patency occurs in the other 25% (Hagen, Scholz & Edwards, 1984). The reasons PFOs fail to close are unknown, but it is currently assumed they are likely related to multifactorial inheritance.

#### **Atrial Septal Defect**

One of the most common adult congenital heart defects, an atrial septal defect (ASD) is a persistent communication between the atria. Much like a patent foramen ovale, an ASD arises from incomplete fusion of the septum primum and septum secundum.

There are several different types of ASDs (see Figure 1):

- Secundum ASD in the region of the fossa ovalis;
- Primum ASD, positioned inferiorly near the crux of the heart;
- Sinus venosus ASD, located superiorly near the superior vena caval entry or inferiorly near the inferior vena caval entry; and
- The uncommon coronary sinus septal defect, which causes shunting into the left atrium via a communication in the superior aspect of the coronary sinus, posterior to the left atrium.

#### **PFO Anatomy and Associated Anomalies**

The autopsy-derived prevalence of PFO is 27% with decreasing prevalence at each decade of life. The PFO is a residual, oblique, slit-shaped defect resembling a tunnel. In adults, the persistent patent foramen ovale slit width ranges from 1 to 19 mm (mean 4.9 mm)

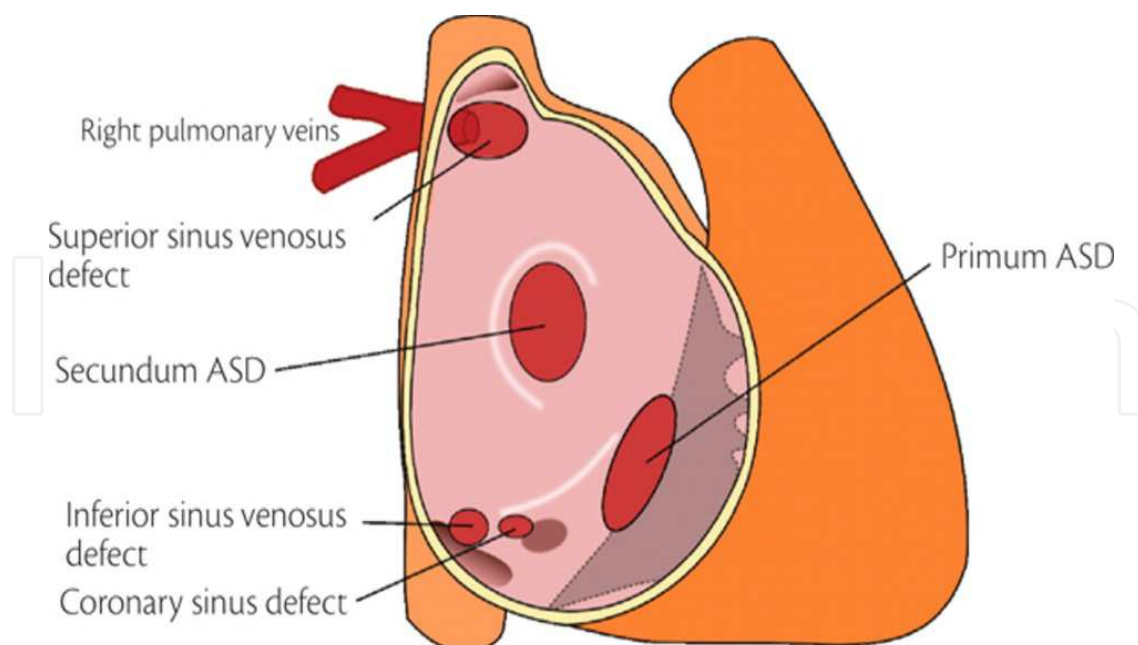


Fig. 1. Types of atrial septal defects. The **European Association of Echocardiography Textbook**.

(Hagen, Scholz & Edwards, 1984). The PFO size increases with age, reflecting size-based selection over time where larger PFOs remain patent and smaller defects close. Greater PFO size increases the risk of paradoxical embolism (Steiner, DiTullio, Rundek et al., 1998). Heterogeneity of size and morphology are pertinent to interventional device closure selection.

The histopathology of the PFO has not been thoroughly addressed in literature, although it is a point of increasing importance as percutaneous closure technologies must interact with these tissues at cellular level. The muscular atrial wall consists of endocardium having endothelium and thick subendothelial layers of connective tissue rich in collagen and elastin. A thicker myocardium lies beneath these structures, with loosely arranged musculature.

PFOs are associated with several anatomic anomalies, most commonly with atrial septal aneurysms (ASA) and Chiari networks.

An ASA represents an aneurysmal dilatation of a part or all of the septum primum, protruding into either atrium. The ASA is defined as phasic septal excursion of at least 10 mm during the cardiorespiratory cycle. M-mode transesophageal echocardiography (TEE) or intracardiac echocardiography is essential for precisely measuring septal excursion of the ASA. A persistent ASA can be isolated finding but generally is associated with other ASDs or a PFO. Fenestrated ASA may present with the clinical findings of an ASD with a significant left to right shunt, especially if there are multiple defects.

The Chiari network is a remnant of the right valve of the sinus venosus, and its role is poorly understood. It originates from a region of the Eustachian and Thebesian valves with attachment to the upper wall of the right atrium or atrial septum. The Eustachian valve is common but it should be distinguished from Chiari networks because it does not attach to

the upper wall of the right atrium or atrial septum, although it may be mobile and fenestrated.

In a study of 1436 adult patients, 83% of patients were found to have both Chiari networks and a PFO, suggesting a strong association. Large right-to-left shunting was found significantly more often in patients with Chiari networks than in controls (55% vs. 12%). This study also found Chiari networks associated with ASAs in 24% of patients. The Chiari network is more common in cryptogenic stroke patients than in patients evaluated for other indications (4.6% vs. 0.5%), and it may facilitate paradoxical embolism (Schneider, Hofmann, Justen et al., 1995).

### **Diagnosis of Patent Foramen Ovale**

A patent foramen ovale may be detected by transthoracic echocardiography (TTE), TEE, transcranial Doppler (TCD), and sometimes by transmitral Doppler. These techniques were compared in studies of proven embolic stroke.

Although the PFO can occasionally be documented in adults with a TTE, the result is rarely unequivocal. TEE, rather than TTE, remains the diagnosis method of choice, due to increased sensitivity.

PFO detection can be augmented by cough or releasing of a sustained Valsalva maneuver, while injecting an aerated colloidal solution into the systemic venous circulation (the bubble test, agitated saline, or contrast study). These maneuvers open the foramen when the right atrium fills with blood from the abdomen, while the left atrium volume is depleted before blood coming through the pulmonary veins, and thus the right atrial pressure exceeds the left atrial pressure.

The Valsalva maneuver is now considered necessary to find right-to-left shunts when performing echocardiography of any type, with or without contrast injection. The physical hole in the atrial wall may not be imaged, but detecting its shunt clearly improves sensitivity and specificity.

TCD is comparable to contrast TEE for detecting PFO-related right-to-left shunts echocardiography and is easy to perform at bedside (Sloan, Alexandrov, Tegeler et al., 2004). TCD has recently been augmented by power M-Mode, a technology that allows power display with Doppler velocity and velocity signals over selectable depth ranges along the transducer beam. TCD M-mode enhances sensitivity to contrast bubble emboli over single-gated examination (Spencer, Moehring, Jesurum et al., 2004; Moehring & Spencer, 2002).

### **Rationale for PFO and ASD treatment in patients with paradoxical embolism**

As mentioned before, approximately 40% of ischemic strokes have no clear etiology (i.e., cryptogenic strokes). Treatment of this particular type of stroke could have a significant impact on decreasing the stroke burden in the general population.

One study of 60 adults under 55 years of age with ischemic stroke compared contrast echocardiographic examinations with 100 normal subjects. PFO prevalence was significantly higher in the stroke group than in controls (40% vs. 10%). PFO was found in 26 stroke patients with no other identifiable cause, and the study concluded that the PFO-induced paradoxical embolism is a cause of stroke (Lechat, Mas, Lascault et al., 1988).

The PFO-ASA Study supports these findings, where 46% of young cryptogenic stroke patients had PFO (Lamy, Giannesini, Zuber et al., 2002).

Cramer et al. evaluated young stroke patients (18 to 60 years old) early after stroke using magnetic resonance imaging venography (Cramer, Rordorf, Maki, et al., 2004). Pelvic deep venous thrombosis was increased in the cryptogenic stroke population compared to controls (20% vs. 4%). The cryptogenic stroke group was significantly younger (42 vs. 49 years) with fewer risk factors for atherosclerosis, such as hypertension and smoking. PFO prevalence was significantly higher in the cryptogenic stroke group than in controls (59% vs. 19%).

A prospective study of 598 patients (ages 18 to 55 years) presenting with cryptogenic stroke showed that 36% had PFO, 1.7% had ASA and 8.5% had both abnormalities. Patients with both PFO and ASA who have had a stroke, are thus at higher risk for recurrent stroke, and preventive strategies other than aspirin should be considered (Mas, Arquizan, Lamy et al., 2001).

Decompression illness in divers is another PFO-associated clinical syndrome. Decompression syndrome (DCS) is categorized in type I and type II. Type I DCS is composed of localized joint pain, musculoskeletal pain, and/or skin rash, and type II DCS consists of neurologic symptoms (limb tingling, paresthesias, severe headache with mental confusion, paraplegia, loss of consciousness, audio vestibular symptoms, and dyspnea with chest pain). The PFO at rest is significantly associated with type II DCS.

In a seminal study, TCD ultrasonography detected a right-to-left shunt in all divers with multiple brain lesions suggesting the presence of a PFO (Knauth, Ries, Pohimann et al., 1997). A comparative investigation regarding brain lesions and the presence of a PFO in sport divers and non-diving controls showed that brain lesions were more common in individuals with a PFO, although divers had more brain lesions than non-divers, irrespective of the presence of a PFO (Schwerzmann, Seiler, Lipp et al., 2001). This has led some diving schools to recommend screening for the presence of a PFO for professional divers or avid amateurs.

The presumed mechanism of cerebral vascular events in patients with a patent foramen ovale or an atrial septal defect is a transient increase in right-sided pressure, which causes a right-to-left shunt. In this scenario, embolization into the left circulation may be produced from a small right-sided thrombus. It is possible, therefore, for paradoxical embolization to occur into other vascular beds such as the coronary artery system and cause an acute myocardial infarction. Few such cases of paradoxical coronary embolisms have been reported in the literature and the diagnosis was made by excluding other sources of coronary artery disease or embolization (Deborah, Gersony, Sang et al., 2001; Agostoni, Gasparini & Destro, 2004).

#### **Medical versus surgical treatment of symptomatic atrial septal defects**

Surgical closure has been demonstrated to be effective in the prevention of recurrent stroke (Mohr, Thompson, Lazar et al., 2001). However, due to the risks and expense of open-heart surgery, subjects are largely treated with oral anticoagulation and antiplatelet agents on an empirical basis.

The present empirical therapy of subjects with PFO and paradoxical embolism is far from ideal and it is uncertain whether anticoagulants such as warfarin and antiplatelet agents are effective as primary or secondary therapy in preventing stroke in patients with PFO.

The PFO in the Cryptogenic Stroke Study Investigators found no difference in primary end-points (recurrent stroke and death) between aspirin and warfarin treatment of PFO patients at two years (Bridges, Hellenbrand, Latson et al., 1992).

The Warfarin-Aspirin Recurrent Stroke Study was a prospective trial of 2206 patients with prior stroke (Homma, Sacco, Di Tullio et al., 2002). Patients were randomized to aspirin (325 mg/day) or warfarin (INR 1.4 to 2.8). After two years, the investigators concluded that there were no significant differences between aspirin and warfarin treatment for recurrent stroke or death. The incidence of recurrent stroke, transient ischemic attacks or death was 17.8 % per year in the warfarin group vs. 16% per year in the aspirin group. Patients with cryptogenic stroke showed no significant benefit in either treatment group.

The incidence of major hemorrhage (per 100 patients per year) was 2.2 in the warfarin group vs. 1.5 in the aspirin group. The authors note that higher target INRs (3.0-4.5) have been associated with excessive rates of major hemorrhage.

Bridges et al. found that despite 32 of 36 subjects being on warfarin therapy before device closure, the recurrence rate of stroke was 50% (Bridges, Hellenbrand, Latson et al., 1992). The appropriate duration of warfarin therapy is unknown and empirical and the incidence of major bleeding events ranges from 1.5 to 11% per year.

### **Catheter-Based PFO and ASD Closure**

Some cerebrovascular events and other systemic arterial emboli, especially in young patients, are presumed to be due to paradoxical embolism through an atrial defect, most frequently a patent foramen ovale (PFO). Closure of such defects is an alternative to life-long anticoagulation.

Initial techniques of percutaneous ASD closure were documented with King's device in 1976 (Mills and King, 1976), Rashkind in the 1980's, and Sideris et al. in the 1990's (Mills and King 1976, Rashkind 1983, Sideris 1990).

Bridges et al. first proposed that PFO closure would reduce the incidence of recurrent strokes and demonstrated a statistically significant effect of PFO closure on a small group of high-risk patients (Bridges, Hellenbrand, Latson et al., 1992). Since then, numerous studies have shown that transcatheter PFO closure with current techniques is safe and seems to protect against recurrent strokes in this patient population (Kramer 2010, Krizanic 2010).

In the 1980s, the Rashkind occluder was introduced and revived the interest in the topic, focusing for the first time on the patent foramen ovale. The Rashkind Clamshell occluder was withdrawn from the market because of high incidence of stress fractures and breakage of arms. The clamshell device was modified by introducing an additional bend of the arms and reintroduced as the CardioSEAL device (1996). Subsequently the CardioSeal device was modified by introducing a self-centering mechanism and was renamed STARFlex (Nitinol Medical Technologies, Boston, Massachusetts, USA) (Kramer 2010).

In 1997, a new self-expanding Nitinol prosthesis was developed by Dr. Kurt Amplatz, which consists of two self-expandable round disks connected to each other with a short waist. Nitinol is a nickel-titanium alloy that has the property of resuming its initial shape when deployed (shape memory) (Krizanic 2010; Masura, Gavora et al., 1997). The Amplatz device was approved by FDA in 2001 for ASD closure and has been widely used since. Several modifications of the Amplatz device were introduced since its original design, such as the Amplatz PFO occluder in 1999 and a cribriform device to occlude multiple or fenestrated ASDs.

In 2000, the CardioSEAL device (NMT Medical, Inc. - Boston, MA) and in 2002, the Amplatz PFO Occluder (AGA Medical Corporation - Golden Valley, MN) became available for PFO closure in high-risk patients in the United States. Both devices were subsequently restricted to use in clinical trials evaluating device closure vs. medical therapy in patients with cryptogenic stroke and patent foramen ovale.

One of the devices used in current clinical trials for PFO closure is the Gore HELEX septal occluder. The HELEX device is made up of a single length nitinol wire covered by a thin membrane of expanded polytetrafluoroethylene (ePTFE). ePTFE (Gore-Tex) is a carbon and fluorine based synthetic polymer that is biologically inert and non-biodegradable in the body.

The configuration of the HELEX device consists of two flexible disks elongated around a central mandrel and delivered through a 9F sheath. The device was FDA approved in 2006 for ASD closure and is currently used in the REDUCE trial for PFO closure (The Gore REDUCE Clinical Study "HLX 06-03; Latson, Zahn & Wilson 2000).

A comprehensive review of the ASD closure devices has been addressed in several other chapters of this book and will not be further discussed.

The Amplatz PFO occluder (AGA Medical Corporation - Golden Valley, MN) is currently the most used PFO closure device.

The Amplatz occluder device consists of a nitinol double disk containing polyester fabric inside the two disks. A thin neck formed by the woven wires connects the two atrial disks. The neck is twisted around its long axis and hence is extendable. The device has to be screwed on to a pusher/puller cable and pulled into the introducer sheath. When pushed out of the sheath, it resumes its double-disk shape instantly. The whole process is fully reversible, as many times as required, up to the moment the device is unscrewed from the pusher/puller cable.

Three sizes of Amplatz PFO closure devices are available and named after the diameter of the right sided disk- 18 mm, 25 mm, and 35 mm. The 18 mm PFO occluder comprises of two 18 mm disks and is meant for small PFOs with a stable septum primum. The 35 mm occluder is destined for large PFOs with atrial septal aneurysm and features a 35 mm disk on the right side and a 28 mm disk on the left side. It requires a 9 French sheath in contrast with the two smaller devices fitting through an 8 French sheath (Meier 2005).

The implantation can be performed with a single femoral venous puncture under fluoroscopy without echocardiographic guidance; however, in most institutions ICE is routinely performed to guide device placement both fluoroscopically and with ICE imaging (Image 1-5).



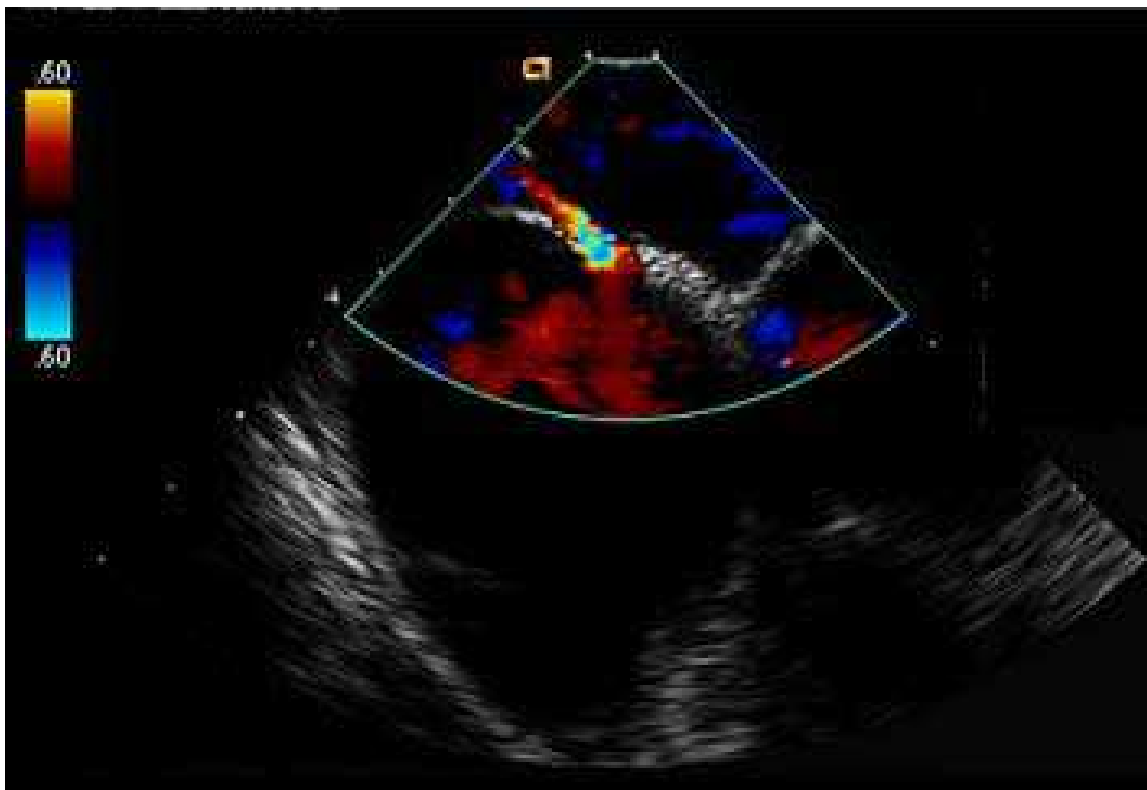


Image 1. ICE imaging of patent foramen ovale with Doppler ultrasound, showing blood flow in the tunnel between the septum primum and septum secundum.



Image 2. ICE imaging of the diagnostic catheter engaging and crossing the tunnel between the septum primum and septum secundum.



Image 3. Positioning of the left atrial disk under ICE guidance, against the left atrial side of the interatrial septum.



Image 4. Positioning of the right atrial disk under ICE guidance, on the right atrial side of the interatrial septum.



Image 5. Pulmonary vein angiogram through the Counard catheter, after crossing the PFO.

The PFO can be crossed by sliding along the septum primum, coming from the inferior vena cava with a wire or a curved catheter. A transvenous sheath (diameter 3 to 5 mm according to the device selected) is placed in to the left atrium (Image 3) and the position of the catheter is documented by pulmonary vein injection (Image 5). The left-sided disk is unfolded and pulled back against the septum, thereby pulling the septum primum against the septum secundum and closing the slit valve (Image 3). The right-sided disk is then deployed and the device released (Image 4). The perfect seat can be assessed before release by echocardiography or by hand-injected dye into the right atrium through the introducer (Image 6-9).

Follow-up treatment includes acetylsalicylic acid (80 to 300 mg) for a few months, with the addition of clopidogrel (75 mg) or warfarin (International Normalized Ratio 2.5 to 3.5) at some centers. Antibiotics during the interventions are commonplace, and prevention against endocarditis is recommended for a few months until the device is completely covered by tissue.

A follow-up transthoracic echocardiogram after a few months with no residual shunting signals the cessation of all treatment and controls.

Technical failures have become extremely rare (for example, inability to cannulate the PFO is less than 1%). Complications may include cardiac tamponade, symptomatic air embolism, loss of device, or puncture site problems.

Complete closure at follow-up can be expected in 90% to 95% of cases with the two US currently available devices. Some trivial residual shunt may be acceptable, albeit undesirable, as the device will act as a filter for particulate matter. Events have recurred in cases where

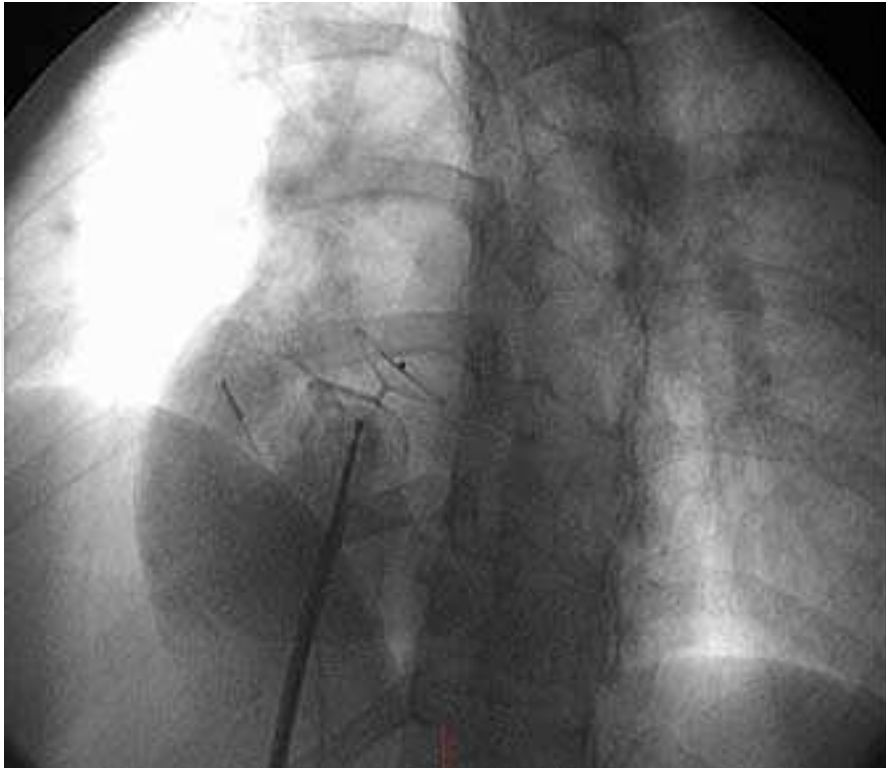


Image 6. Deployed PFO occluder under fluoroscopy, before the retrieval of the delivery catheter.

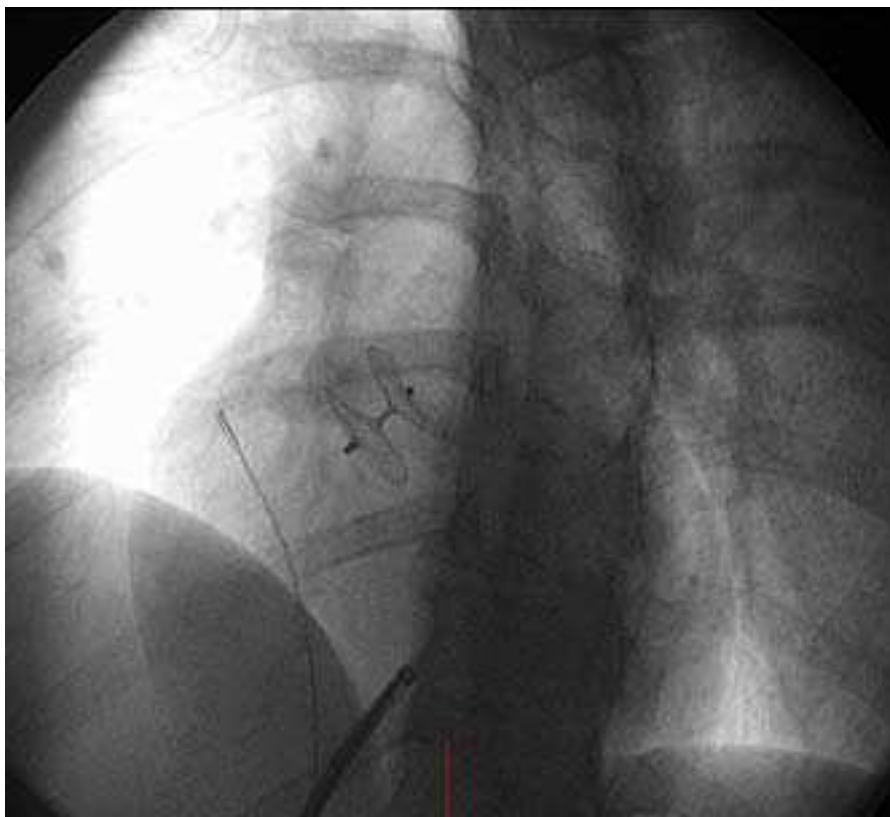


Image 7. Fully deployed PFO occluder under fluoroscopy.

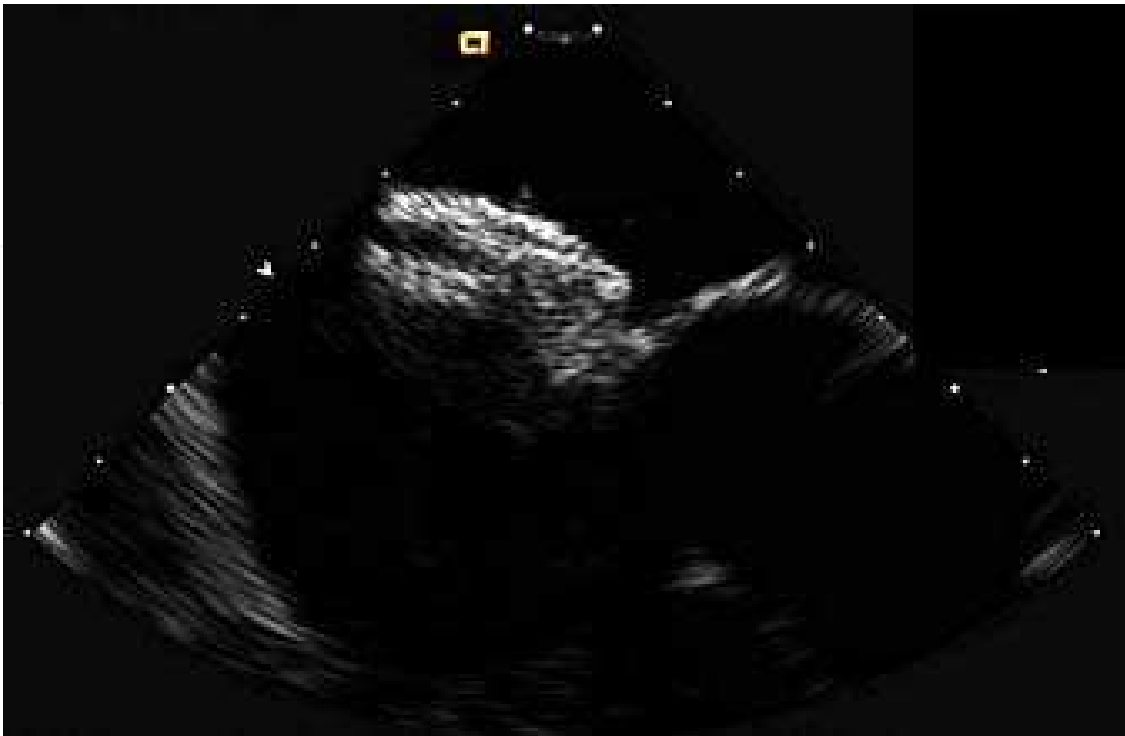


Image 8. Deployed PFO occluder under ICE imaging.

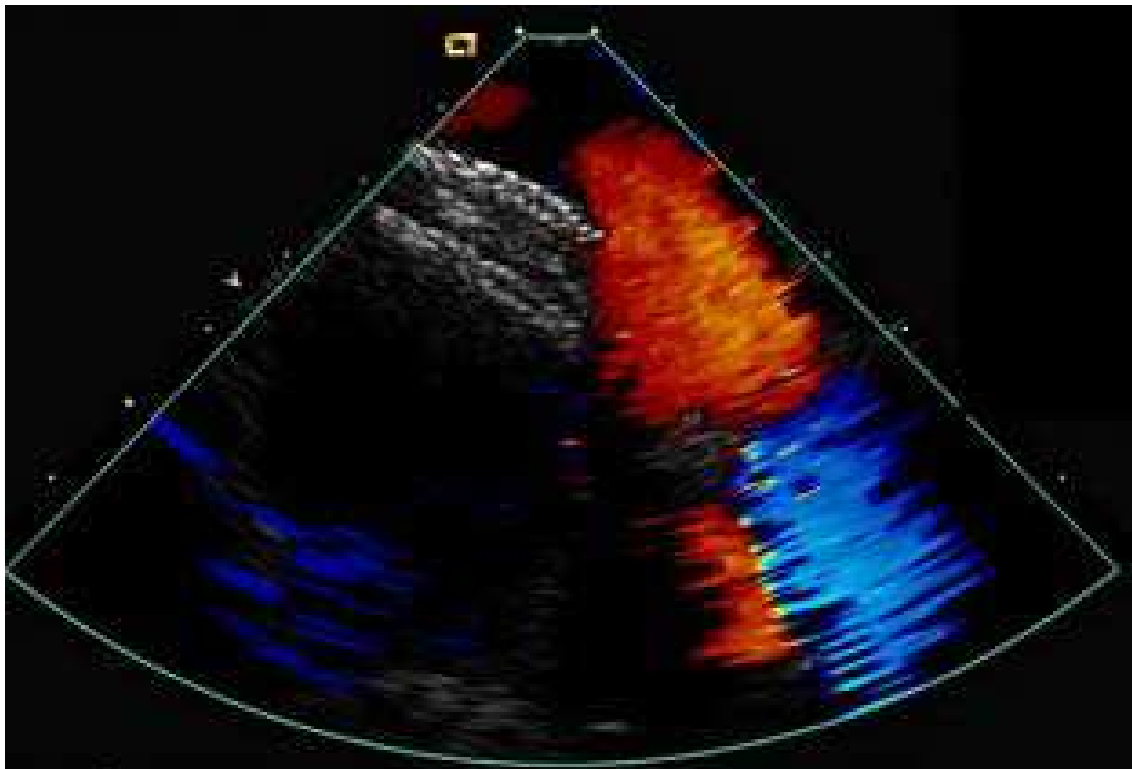


Image 9. Doppler image of a successfully deployed PFO occluder, with significant reduction in the interatrial shunt and no obstruction of the superior vena cava flow.

the PFO was not responsible for the index event, in cases where small emboli formed on the left side of the device, or in cases where closure is incomplete (Wahl, Meier, Haxel et al.,

2001). Thrombosis on the device has been found in about 6% of devices used for PFO closure at one month TEE control in 1000 patients, except for the Amplatzer PFO occluder where it was found in less than 1% (Khairy, O'Donnell & Landzberg 2003).

Pooling the results of the published studies on percutaneous PFO closure, it appears that the intervention yields favorable clinical results over the conservative treatment. Until recently, what came closest to a randomized trial was a matched control follow up study in about 300 patients, of which half were arbitrarily sent for PFO closure by neurologists and half were treated conservatively by the same physicians. Already at a follow up of four years, there was a trend in favor of device closure with an average of 5% events per year (counting all neurological or peripheral symptoms) compared with 7% in the conservative group. This advantage was significant in terms of major strokes, which only occurred in the conservative group. It was also significant in the subgroup of patients who had had more than two events before treatment allocation as well as in those who had complete closure at the six month follow up TEE in the device group (Windecker, Wahl & Nedeltchev, 2004). The few randomized trials in this field have, for years, struggled to enroll sufficient numbers of patients, owing to a variety of factors, including off-label device use.

## CLOSURE I

CLOSURE I was the first completed, randomized, and controlled trial comparing the safety and efficacy of percutaneous PFO closure plus medical therapy versus medical therapy alone for secondary TIA and stroke prevention in patients with PFO (CLOSURE I Trial, 2010). CLOSURE I enrolled 909 patients randomized equally to PFO closure using the STARFlex closure device (NMT Medical, Inc. - Boston, MA) as well as six months of aspirin and clopidogrel (and an additional 18 months of aspirin) or to best medical therapy – aspirin or warfarin or a combination. The original endpoint was the 2-year rate of TIA, stroke, or death. Based on a conservative estimate of the expected event rate (6%) from the literature available before 2003, CLOSURE I was originally designed to enroll 1600 patients. However, after 4 years (2003–2006), CLOSURE I had recruited only 611 patients. In April 2007, the FDA approved a proposed revision to the statistical plan that decreased the sample size from 1600 to 800 patients based on an expected event rate of 6% in the medical arm and 2% in the device arm. Patients with cryptogenic TIA or stroke within 6 months and a PFO were screened for study eligibility under the direction of a treating neurologist. To be included, a PFO must have been documented by TEE and amenable to percutaneous closure with STARFlex. For patients randomized to the device arm, the STARFlex device was implanted via percutaneous intervention. The implant procedure was scheduled as soon as possible from the point of randomization, preferably within 1 week. Either TEE or ICE was used during placement of the device.

In the device arm, patients followed a standardized antiplatelet regimen of clopidogrel 75 mg daily for 6 months plus aspirin for the duration of the trial. Patients randomized to medical therapy were treated with one of the following medications throughout the duration of the study: (1) warfarin with a target International Normalized Ratio of 2.0 to 3.0 with an ideal target of 2.5; (2) aspirin 325 mg daily; (3) aspirin 81 mg daily only,

allowed for documented gastrointestinal intolerance; or (4) aspirin 81 mg daily with warfarin. Clopidogrel, ticlopidine, and aspirin plus extended-release dipyridamole were not allowed in the medical arm. Heparin was permitted during the initial warfarin treatment period to provide sufficient anticoagulation. At two years, the composite primary endpoints, as well as rates of stroke or TIA alone, were no different between groups. An analysis of outcomes according to baseline characteristics, including shunt size or presence/absence of atrial shunts, also found no differences between groups. Both major vascular complications and atrial fibrillation, mostly periprocedural, were significantly more common in the intervention group, but other safety endpoints were no different between study arms. Procedural and technical success rates (no or trace residual leaking) were suboptimal, with only 86.7% percent of PFOs closed at one year. The majority of the adverse events occurred in the device arm during implantation, raising concerns regarding device delivery techniques by the investigators, as this issue has not arisen in larger trials.

### **REDUCE**

REDUCE is an FDA approved prospective, randomized, multicenter, international trial designed to demonstrate the safety and effectiveness of the Gore Helex Septal Occluder for PFO closure in patients with a history of cryptogenic stroke or imaging-confirmed transient ischemic attack. The FDA approved the Gore Helex Septal Occluder for treatment of atrial septal defect in 2006. The ongoing study includes up to 50 investigational sites in the US and Europe. The Gore REDUCE Study investigators aim to address the CLOSURE I limitations by design- all TIAs must be confirmed by neuroimaging studies such as MRI, which will prevent the inclusion of spurious neurological events that are not vascular in origin. Patients with non-cryptogenic strokes or with a substantial burden of vascular risk factors will be excluded from the trial and a uniform medical therapy regimen will be applied for both test and control subjects (The Gore REDUCE Clinical Study "HLX 06-03").

### **RESPECT**

The RESPECT trial is a randomized, multi-center study investigating whether closure of PFOs using the AMPLATZER PFO Occluder device is safe and effective compared to current standard-of-care treatment in the prevention of a cryptogenic stroke. The RESPECT trial started recruiting patients in 2003 and completed enrollment in January 2012. According to St Jude, RESPECT has enrolled 980 patients over its eight years running, yielding more than 2300 patient-years of data.

The trial is designed to continue until sufficient events have accumulated to be able to assess treatment effectiveness. By protocol, patients enrolled in the trial will continue to be followed until regulatory approval is granted by the FDA, thus providing substantial long-term follow-up on this patient population (RESPECT PFO Clinical Trial).

## **2. Conclusion**

The indication for PFO closure in the face of paradoxical embolism has been widely accepted in the presence of an atrial septal aneurysm or after several embolic events, outside the United States.

Some clinicians choose to close patent foramen ovale in patients with high-risk features, such as stroke despite adequate aspirin or warfarin therapy, large right-to-left interatrial shunts or presence of atrial septal aneurysm.

If the current randomized clinical trials will favor device closure in the setting of paradoxical embolism, it is likely that percutaneous PFO closure will increase significantly in the United States.

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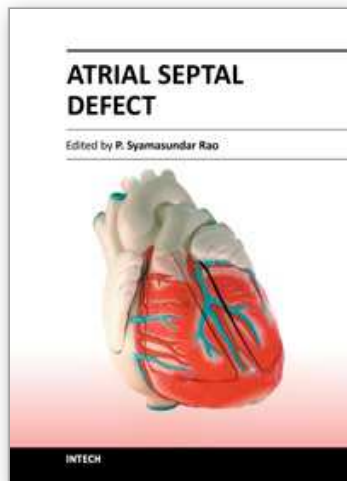
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### **Atrial Septal Defect**

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Atrial Septal Defects (ASDs) are relatively common both in children and adults. Recent reports of increase in the prevalence of ASD may be related use of color Doppler echocardiography. The etiology of the ASD is largely unknown. While the majority of the book addresses closure of ASDs, one chapter in particular focuses on creating atrial defects in the fetus with hypoplastic left heart syndrome. This book, I hope, will give the needed knowledge to the physician caring for infants, children, adults and elderly with ASD which may help them provide best possible care for their patients.

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