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Percutaneous treatment of patent foramen ovale and atrial septal defects.

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Authors
Tobis, J
Shenoda, M

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Percutaneous treatment of inter-atrial septal defects has undergone exponential growth in the past 2 decades. Improved percutaneous devices and interventional techniques with low complication rates make this procedure an attractive therapeutic option for congenital atrial septal defects (ASD). Although indications for catheter-based ASD closure are well-documented, those for catheter-based patent foramen ovale (PFO) closure are still evolving. Results from 2 randomized clinical trials question the benefit of percutaneous PFO closure, but concern has also been raised about the efficacy of the device used in those trials. This review will focus on the anatomy, associated syndromes, detection, and data for percutaneous closure of both PFOs and ASDs. (J Am Coll Cardiol 2012;60:1722–32) © 2012 by the American College of Cardiology Foundation

Percutaneous treatment of inter-atrial septal defects has opened new areas of research, because unexpected associations have been uncovered. Improved devices, interventional techniques, and low complication rates make this procedure an attractive therapeutic option for congenital atrial septal defects (ASD). In the United States, the rates of annual percutaneous patent foramen ovale (PFO) and ASD closures have increased nearly 50-fold over the past decade. Although indications for catheter-based ASD closures are well-documented by many society guidelines, those for catheter-based PFO closure are still evolving. The results of 2 recent randomized clinical trials raise questions about the utility of percutaneous PFO closure. This review will focus on the anatomy, physiology, associated syndromes, detection, and data for percutaneous closure of both PFOs and ASDs.

**Patent Foramen Ovale**

**PFO anatomy.** The fetus depends upon oxygen that is transferred in utero from the maternal circulation across the placenta. Because the fetal lungs are not capable of oxygenating blood, the immature lungs are bypassed via a communication between the atria at the foramen ovale. Oxygenated blood is directed from the inferior vena cava to the superior aspect of the right atrium (RA) via the Eustachian valve, then crosses the foramen ovale into the left atrium (LA) and enters the systemic circulation (Fig. 1, Online Videos 1 and 2).

At the time of birth, right heart filling pressures and pulmonary vascular resistance decrease, leading to higher LA pressures, and closure of the foramen ovale flap against the septum secundum. The contact between the septum primum flap and the septum secundum leads to fusion of these tissues and permanent closure of the foramen ovale, a process that is usually completed within the first year of life. The foramen ovale flap fails to fuse in approximately 20% of humans, which leads to persistent patency. Because PFOs aggregate in families, it is hypothesized that closure of the PFO is in part determined by genes such as Notch 3, which is associated with embryologic control of the septum and is deficient in the cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) syndrome in which there is a high frequency of PFO, migraine, and leukoencephalopathy.

**Physiology of right-to-left shunting through a PFO.** In the basal state, the LA pressure is higher than RA pressure, so the septum primum flap of the PFO is pressed against the septum secundum, which keeps the foramen ovale closed. However, if the RA pressure exceeds the LA pressure, blood can then flow from the RA to the LA. This occurs frequently when a person coughs, laughs, sneezes, takes a deep breath, or upon release of the Valsalva maneuver, which increases the return of venous blood to the RA (Fig. 2, Online Videos 3 and 4). Approximately 5% of patients with stroke or migraine have a history of vigorous straining or exercising immediately before their event.

**PFO associated syndromes. CRYPTOGENIC STROKE.** Paradoxical embolism through a PFO was first described in 1877 by Julius Cohnheim during an autopsy of a young woman with a fatal occlusion of a cerebral artery. He observed that the patient had a significant lower extremity thrombus and a large PFO, which he hypothesized served as
a conduit for an arterial embolism that paradoxically started in the venous circulation. The advent of echocardiography improved the understanding of PFO anatomy and detection. In 1988, several observational studies emphasized the association of a PFO with cryptogenic stroke (where there is no identifiable cause for the stroke) in young patients (1,2). With contrast echocardiography, the prevalence of a PFO in patients under the age of 55 with cryptogenic stroke was 54% (1). Other studies consistently corroborate the association of PFO and cryptogenic stroke even in older patients with stroke of unknown etiology (3,4). There are approximately 140,000 cryptogenic strokes/year in the United States, and 50% of them have a PFO, so it is estimated that the risk of developing a stroke in someone with a PFO is 1 in 1,000/year. The recurrence rate in patients with a PFO who have already suffered a stroke is approximately 2% annually. Higher stroke rates (15%) have been associated with the presence of an atrial septal aneurysm (ASA). The mechanism for the increased risk of paradoxical embolism in patients with an ASA and PFO was initially thought to be due to thrombus formation on the redundant interatrial tissue, but this has not been documented, despite intensive investigation with transesophageal echocardiography (TEE). The current theory is that an ASA permits greater flow and therefore increases the chance of a thrombus passing from the venous to the arterial circulation (5–7).

Although it is logical to assume that larger PFOs would be associated with an increased frequency of cryptogenic stroke or a larger stroke burden, the data have been conflicting. There is a loose correlation between stroke volume on magnetic resonance imaging and PFO size on cardiac echocardiography, but there is wide overlap, and it is possible for a large stroke to occur with a small PFO (8). Thus, PFO size and anatomy should not be the criteria to determine whether a PFO should be closed.

Venous thrombosis is believed to be the source of paradoxical embolism in cryptogenic strokes associated with PFOs. However, the incidence of detectable veno-occlusive disease in the lower extremities and pelvis is low. Magnetic resonance imaging venograms in patients with cryptogenic stroke demonstrate a higher incidence of pelvic thrombosis compared with patients with strokes of identifiable causes (20% vs. 4%, p < 0.03) (9). Small emboli might be shed from small varicose veins or hemorrhoids and might not be detected by current imaging modalities.

Observational studies suggest that medical treatment with antiplatelet or antithrombotic agents lowers recurrent event rates. However, in the WARSS study (Warfarin Aspirin Recurrent Stroke Study), there was no difference in the recurrence rate of stroke in patients who were taking warfarin or aspirin, but the recurrence rate was high in both groups at 8%/year (10). A substudy of this trial assessed the recurrence rate in patients who had TEEs (PICSS [Patent Foramen Ovale in Cryptogenic Stroke Study]) (11). The recurrence rate at 2 years was 2.7 times higher in patients >65 years of age who had a PFO (38%), compared with those people with cryptogenic stroke who did not have a PFO (14%).

**STUDIES OF PFO CLOSURE FOR CRYPTOGENIC STROKE.** As distinguished from medical therapy, surgical closure of PFO in 193 patients with cryptogenic stroke showed a recurrent annual stroke risk of only 0.42% and transient ischemic attack (TIA) risk of 0.56%. A pooled analysis of 24 studies comprising 3,819 patients who had percutaneous PFO closure suggests a recurrent annual stroke risk of 0.47% and recurrent TIA risk of 0.85%. On the basis of these observations, it was predicted that a randomized trial would prove that PFO closure was preferable to medical therapy to prevent recurrent cryptogenic stroke.

The CLOSURE I trial (Evaluation of the STARFlex Septal Closure System in Patients With a Stroke or TIA Due to the Possible Passage of a Clot of Unknown Origin Through a Patent Foramen Ovale [PFO]) was the first randomized clinical trial evaluating the effects of PFO closure on recurrent cryptogenic stroke and TIA versus medical therapy. This was a superiority trial that randomized 909 patients with a history of cryptogenic stroke to percutaneous PFO closure with a STARFlex PFO device versus medical therapy with warfarin (international normalized ratio goal 2.0 to 3.0), aspirin 325 mg alone, or aspirin 81 mg plus warfarin. The results did not demonstrate a benefit of PFO closure with the STARFlex device compared with medical therapy. The primary composite endpoint of a reduction in stroke, TIA, and mortality at 2 years was reached in 5.9% of patients in the device arm and 7.7% of patients in the medical treatment arm (p < 0.30). Individually, stroke (3.1% vs. 3.4%) or TIA (3.3% vs. 4.6%) was not statistically different between the 2 treatment arms. Device closure was successful in only 87% of cases, which is similar to previous device closure studies with the STARFlex device but lower than that reported for other PFO closure devices. Major vascular complications (3.2%) and atrial fibrillation (5.7%) were significantly higher in the device group (p < 0.001 for both).

There were several potential explanations for this contradiction between the observational reports and this first randomized clinical trial of PFO closure for cryptogenic

**Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
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<tr>
<td>AHA</td>
<td>American Heart Association</td>
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<tr>
<td>ASA</td>
<td>atrial septal aneurysm</td>
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<tr>
<td>ASD</td>
<td>atrial septal defect</td>
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<tr>
<td>ASO</td>
<td>Amplatzer Septal Occluder</td>
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<tr>
<td>BCP</td>
<td>birth control pills</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>HSO</td>
<td>Helex Septal Occluder</td>
</tr>
<tr>
<td>LA</td>
<td>left atrium/atrial</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
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<tr>
<td>OSA</td>
<td>obstructive sleep apnea</td>
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<tr>
<td>PFO</td>
<td>patent foramen ovale</td>
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<tr>
<td>RA</td>
<td>right atrium/atrial</td>
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<tr>
<td>TEE</td>
<td>transesophageal echocardiogram</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
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<tr>
<td>TTE</td>
<td>transthoracic echocardiogram</td>
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<tr>
<td>WML</td>
<td>white matter lesion</td>
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Approximately 2% of patients experience a recurrent stroke each year. This number is important because it is relatively low, making it difficult to power randomized trials with adequate statistical power. To adequately power a study with clinically significant endpoints requires a large number of patients and long-term follow-up (≥5 years). In addition, these trials are taking place in an unusual environment for new device technology. When a new device is developed, it usually is not available to the public unless they participate in a randomized trial. However, the U.S. Food and Drug Administration (FDA) has approved several devices for closure of ASDs that can be used effectively to close a PFO off-label. Many patients and referring physicians prefer to have the PFO closed definitively rather than participate in a randomized trial in which there is a 50% chance of receiving medical therapy. Even though there is no scientific proof that PFO closure is preferable to medical treatment, patients who have had a stroke are anxious that they will suffer another event and often prefer the certainty of an intervention over medical therapy. This is especially ironic, because the initial results of the CLOSURE I trial suggest that there is equality in distribution between these 2 treatment options. These concerns result in a self-selection bias, because patients at high risk of recurrent stroke are less likely to be enrolled in the randomized clinical trials. These daunting problems should be taken into consideration when evaluating the ultimate results of current PFO stroke trials.

ASSOCIATION OF MIGRAINE HEADACHE AND PFO. The prevalence of migraine is 18% in women and 6% in men. The neurobiology of migraine headache disorders has yet to be fully elucidated. Previous theories with regard to the etiology of migraines hypothesized that cerebral vasospasm...
led to brain ischemia and directly produced migraine auras. In addition, stroke associated with migraine was believed to be secondary to such intense arterial constriction that a cerebral infarction ensued directly from the vasospasm. Magnetic resonance imaging and positron emission tomography have subsequently demonstrated that cerebral vasodilation occurs first, followed by vasoconstriction that is associated with cortical neuronal depression. This inhibition of neurons spreads as a wave from the optical cortex to the motor and sensory cortices, leading to transient neurological deficits that are identified as migraine auras. This more recent concept of migraine has been demonstrated in elegant experiments with a mouse transgenic model of human genes associated with familial migraine and hemiplegia due to abnormalities in calcium or sodium channel proteins (14).

Given this current concept of migraine physiology, it is hypothesized that a PFO serves as a conduit for the passage of chemical triggers that interact with neuronal receptors in susceptible people. These triggers induce cortical depolarization and concomitant transient neurological deficits, leading to the clinical phenotype of auras and migraine headache. The PFO permits the chemical triggers to reach the brain without entering the pulmonary circulation where degradation of these products would normally occur. Migraines have also been induced in a mouse model by injecting particles that embolize to the brain (15).

The initial reports associating migraine headaches with aura and PFO disclosed a prevalence of right-to-left shunting by transcranial Doppler of 41% to 48%, compared with 16% to 20% in control subjects (16,17). The association of PFO closure and the cessation of migraine headaches was first published in 2000 by Wilmshurst et al. (18) as an incidental finding while studying the effects of PFO closure on people with decompression illness. In 37 of these patients who also had migraine headaches, 45% reported cessation of their headaches after PFO closure.

In addition to the close association of PFO and migraine with aura, there is also a higher risk of stroke in patients with a history of migraine. A meta-analysis of 14 studies revealed a 2-fold increased risk of ischemic stroke in migraine patients, compared with people without migraine (19). Those individuals with associated aura had a relative risk of 2.27, compared with 1.83 in those without aura. It is hypothesized that this increased risk of ischemic stroke in migraineurs is due primarily to the mechanism of paradoxical embolism through a PFO. Wilmshurst et al. (20) documented a high incidence of PFO (84%) in migraineurs who had suffered a stroke, compared with migraineurs without a history of stroke (38%). We believe this concept also explains the 8-fold higher incidence of stroke in migraineurs who use birth control pills (BCPs) or the 15-fold higher risk in migraineurs who smoke tobacco and use BCPs. The postulated mechanism is that BCP or smoking tobacco predisposes to venous thrombus, and the presence of the migraine identifies those people with a higher likelihood of having a PFO, so both the thrombus and the passageway are present in these subsets.

**STUDIES OF PFO CLOSURE IN MIGRAINEURS.** Over the past decade, there have been 17 reported observational studies evaluating the effect of percutaneous PFO closure on migraine headaches. A pooled analysis of these 866 people reveals that 83% had either complete cessation of migraines or a clinically significant reduction (defined as >50% reduction in headache days/month). The number of patients suffering from migraine with aura who responded was approximately 2-fold greater than those who had migraine without aura.

The only completed randomized trial of PFO closure for migraine headaches is the MIST (Migraine Intervention with STARFlex Technology) Trial. The MIST trial enrolled 147 patients who were randomized 1:1 to device closure with the STARFlex septal implant (NMT Medical) or a sham procedure consisting of a skin incision in the groin under general anesthesia. Patients averaged 5 migraine attacks/month with 30 headache days over a 3-month period. After 6 months, the primary endpoint of complete cessation of migraine headaches after device closure was not reached, because only 3 patients in each group reported no further migraine headaches. The secondary endpoints, which included the incidence, frequency, and severity of migraine attacks were also not met in this trial.

The MIST trial has been extensively critiqued for methodological design and credibility. The patient population enrolled included those with chronic headaches, a subgroup that might not respond to conventional therapies, because the headache etiology is obscured with over-medication and drug withdrawal headache. The procedural complications were 6.8% in the MIST I trial, which is higher than that reported in multiple observational studies. The follow-up period of 3 to 6 months might be too brief, because percutaneous PFO closure devices might require more time to endothelialize and eliminate shunting through a PFO. Only contrast transthoracic echocardiograms (TTEs) were obtained at follow-up, which is less sensitive than TEE or transcranial Doppler detection of right-to-left shunting. There is also significant controversy about the true incidence of residual shunts, which damages the credibility of the study. Although the MIST I trial reported a 5% residual shunt in the device arm at 6 months, one of the principle investigators alleges that 35% of device-treated patients had a large residual shunt. Given that there was no independent echocardiography core laboratory, these allegations are matters of concern and require cautious interpretation of the MIST trial.

The ongoing PREMIUM Migraine Trial (Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the Amplatzer PFO Occluder to Medical Management) might elucidate the role of PFO closure in migraine patients. This is a randomized, sham-controlled trial evalu-
inating the effectiveness of percutaneous PFO closure with the Amplatzer PFO Occluder (St. Jude Medical, Plymouth, Minnesota) versus a sham procedure plus standard medical therapy. This trial might address the shortcomings of the MIST I trial by enrolling a more appropriate patient population (excluding patients with chronic headaches), use of a more effective closure device with less complications, and extended follow-up (1 year) with trans-cranial Doppler and TEE evaluation of the implanted device.

**PLATYPNEA-ORTHODEOxia SYNDrome.** Platypnea-Orthodeoxia is a rare syndrome consisting of hypoxemia and shortness of breath upon assuming an upright position. It is believed that anatomic changes with age, such as uncoiling of the aorta, diaphragmatic paralysis, stretch of the atrial septum, and increase shunting through a PFO, produce significant desaturation of arterial blood when the patient stands up or bends over. Landzberg et al. (21) first described relief of symptoms and reversal of arterial desaturation in this syndrome after transcatheter closure of PFOs in 8 patients. More recently, a French registry of 78 patients reported a significant increase in oxygen saturation and dyspnea improvement immediately after percutaneous PFO closure (22).

**MYOCARDIAL INFARCTION WITH NORMAL CORONARIES.** The incidence of myocardial infarction (MI) with normal coronary arteries is reported to be between 1% and 7% of patients who present with cardiac enzyme documented MI. A PFO might serve as the passageway for a venous thrombus that embolizes to a coronary artery. Additionally, coronary vasospasm might occur from vasoactive substances, such as serotonin, that could pass unaltered through a PFO and have a direct effect on the coronary vasculature. This hypothesis is difficult to prove but should be considered in the select patient population of young people with an MI but no atherosclerosis.

**DECOMPRESSION SYNDROME.** Decompression illness is caused by nitrogen microbubbles formed in the vasculature as a result of a reduction in environmental pressure. Symptoms are usually constitutional and nonspecific. The rate of occurrence has decreased due to improved decompression procedures but still affects approximately 1,000 divers/year. The risk of developing decompression illness is 5- to 13-fold higher in individuals with a PFO (23,24). Wilmshurst et al. (25,26) first reported a decreased incidence of decompression syndrome in divers after transcatheter closure of PFOs. Since then numerous reports have followed, with long-term prevention of this syndrome. No specific guidelines exist for PFO closure in people who have decompression illness, but the options are to stop diving, decrease the depth or time of dives, or undergo percutaneous PFO closure.

**HIGH ALTITUDE PULMONARY EDEMA.** Although the exact pathogenesis of High Altitude Pulmonary Edema has yet to be clarified, PFO has been implicated as a contributing factor. Allemann et al. (27) reported a 4-fold increased frequency of PFO in individuals susceptible to developing high altitude pulmonary edema, compared with those who were resistant. The degree of arterial hypoxemia correlated with PFO size. The proposed patho-physiology entails a cycle of high altitude hypoxia producing pulmonary vasoconstriction and hypertension. In the presence of a PFO, there is increased right-to-left shunting, leading to worsening arterial hypoxemia, altered alveolar-arterial gradients, and capillary leakage with pulmonary edema. Elimination of right-to-left shunting via percutaneous PFO closure has been reported in anecdotal cases to have benefits (28).

**OBSTRUCTIVE SLEEP APNEA EXACERBATION.** It is estimated that 5% of U.S. adults are affected by obstructive sleep apnea (OSA), which is associated with significant morbidity and has been linked to various cardiovascular conditions. The prevalence of a PFO in adults with OSA is significantly higher than the general population and has been reported to be as high as 69% (29). Those with OSA and a PFO have significantly lower arterial oxygen saturation after periods of sleep apnea compared with those without a PFO. It is postulated that the underlying mechanism for these observations involves hyperventilation-induced hypoxic pulmonary vasoconstriction, leading to elevated right heart filling pressures and increased right-to-left shunting through the PFO. There are several reports of significant improvements in symptoms and arterial saturation in OSA patients who have undergone PFO closure (30,31). Although these initial reports are encouraging, a randomized trial of PFO closure would be appropriate before it is recommended to close PFOs in OSA patients.

**CEREBRAL WHITE MATTER LESIONS.** White matter lesions (WMLs) are defects of the neuronal axons where myelin is replaced by central nervous system fluid (Fig. 3). Histologically, WMLs demonstrate demyelination, axonal loss, and astrocytic gliosis. Although the pathophysiology of these brain lesions remains obscure, they have been linked to an increased stroke risk, personality changes, and dementia associated with Alzheimer’s disease. Hypotheses with regard to the mechanism of WML formation include focal cerebral hypoperfusion due to spasm, metabolic imbalances due to migraines with aura, microvascular ischemic changes, and/or embolic phenomena from right-to-left shunting (32). A meta-analysis of 7 studies found a 4-fold increase of WMLs in migraine patients compared with a control group (33). Of our patients with PFO without migraine, who also had magnetic resonance imaging, one-third demonstrated WMLs. Thus there might be multiple causes of these brain abnormalities that include metabolic and embolic pathways.

**PFO Detection.** Contrast TTE is usually the initial diagnostic modality for the detection of intracardiac shunts. However, TTE lacks the sensitivity and specificity of TEE, which has better image resolution, especially of posterior heart structures such as the interatrial septum. Although a right-to-left shunt might occur at rest, the detection of shunting usually requires a Valsalva maneuver, which en-
hances the detection of interatrial shunting by 3- to 4-fold. Limitations of TEE imaging in the detection of right-to-left interatrial shunts include operator experience, difficult imaging planes, and lack of an adequate Valsalva maneuver because of sedation and the presence of the tube in the oropharynx. Transcranial Doppler is a noninvasive procedure that detects contrast microbubbles passing through the middle cerebral artery. Transcranial Doppler has been reported to have greater sensitivity for the detection of a PFO compared with TEE. Our center uses transcranial Doppler as the preferred screening method and TEE or intracardiac echocardiography to distinguish pulmonary from intracardiac shunts.

Percutaneous PFO closure complications. Percutaneous PFO closure is a relatively safe procedure and frequently is performed on an outpatient basis. Observational studies of transcatheter PFO closure have reported a major complication rate between 0.2% and 1.5% (34,35) for procedural-related death, hemorrhage requiring transfusion, cardiac tamponade, and fatal pulmonary emboli. Minor complications including peri-procedural atrial arrhythmias, device arm fractures, device embolization, thrombosis, and femoral hematomas range from 7.9% to 11.5% (34,35). Newer percutaneous devices and smaller catheters have led to a decrease in reported major and minor complications.

The incidence of atrial fibrillation after device closure of a PFO is estimated to be 2.5% annually (36), but this depends on the device used. The CardioSEAL-STARFlex device has up to a 7% incidence of post-procedural atrial tachyarrhythmias. Larger Amplatzer devices (>33 mm) have also been associated with increased rates of post-procedural atrial fibrillation.

NICKEL ALLERGY AND MIGRAINE HEADACHES AFTER ATRIAL DEFECT CLOSURE. A transient and paradoxical increase in migraine headaches in a minority of patients immediately after percutaneous PFO or ASD closure is well-documented. This has been attributed to enhanced inflammation induced by the device, especially if the recipient has a nickel allergy (37), which affects 15% of the general population. A local inflammatory reaction on the LA side might lead to platelet activation and release of serotonin or other potential chemical triggers of migraine. This hypothesis is supported by the observation that clopidogrel or steroids often reduce the post-procedural migraines. In addition, these patients might also experience chest discomfort and palpitations, presumably due to local inflammation, nickel sensitivity, or formation of fibrous scar tissue. These side effects might take 3 to 6 months to resolve but on occasion might be so severe that the patient requests removal of the device.

DEVICE EXPLANTATION. Once the device has been in place for several months, scar tissue forms and surgery is required to explant the device. A multi-center survey of 13,736 percutaneous PFO device implants revealed an incidence of surgical removal of 0.28% (38). Explantation was noted to be device-specific, because the CardioSEAL device had a 4 to 5 times higher rate of surgical removal compared with Amplatzer and Gore Helex devices. The CardioSEAL devices were removed primarily due to residual shunts or thrombus formation.

Future directions. Until randomized clinical trials demonstrate positive results, the role of PFO closure will remain undefined. Even if the stroke trials are inconclusive due to difficulty with enrollment, patients who have had a stroke are likely to continue to want their PFO closed off-label. If the PREMIUM migraine trial or the RESPECT or REDUCE stroke trials demonstrate a significant benefit of PFO closure, it could lead to a dramatic rise in the frequency of this intervention. Other conditions that might be associated with right-to-left shunting through a PFO continue to be investigated, and observations concerning PFO will provide exciting areas of research for years to come.

Transcatheter Treatment of ASD

ASD introduction. This discussion will be limited to secundum ASDs, which are one of the most common forms of congenital heart disease. The incidence of ASD is estimated to be 1 in 1,500 live births and accounts for 30%...
to 40% of congenital defects presenting in adulthood. Females are affected twice as often as males.

Although the majority of ASDs are sporadic, genetic syndromes such as Holt-Oram and Ellis van Creveld suggest that an inheritable component is involved in the formation of these interatrial defects. Mutations in the NKK2-5 gene, a cardiac homeobox gene involved in normal cardiac development, are responsible for an autosomal dominant familial ASD that is commonly associated with atrioventricular block (39,40). Sporadic ASDs are also associated with NKK2-5 gene mutations, although these have low penetrance and are not usually associated with atrioventricular block.

**ASD anatomy.** A deficiency of the inter-atrial septal structure can present in several different forms (Fig. 4). Ostium secundum ASDs account for approximately 75% of septal defects. The majority of secundum ASDs result from excessive resorption of the atrial septum primum, resulting in a deficient or absent fossa ovalis area. Absence or underdevelopment of the superior limbus of the septum secundum accounts for a minority of ostium secundum ASDs, and is likely the result of a distinctive morphogenetic process. Although the size and shape of secundum ASDs vary greatly, the vast majority of these defects are amenable to transcatheter closure. Other types of interatrial defects such as ostium primum, sinus venosus, or coronary sinus defects are usually not amenable to catheter-based closure (Fig. 4).

**ASD pathophysiology.** The degree of interatrial shunting is dependent upon the compliance of the right and left ventricles, the systemic and pulmonary circulation resistance, and the size of the defect. Larger ASDs lead to nearly equal RA and LA pressures, and therefore left-to-right shunting depends on the higher right ventricular compliance compared with the left ventricle. Volume overload of the right-sided structures leads to dilation of the RA, right ventricle, and pulmonary system. Chronic left-to-right shunting in adults might lead to mild-to-moderate pulmonary hypertension, the single most influential factor in the clinical course of ASD (41). However, ASDs are not likely to produce the classic Eisenmenger’s syndrome seen with ventricular septal defect. Cases of severe pulmonary hypertension in ASD patients are possibly due to simultaneous primary pulmonary hypertension. In addition, atrial arrhythmias, most commonly atrial flutter/fibrillation, occur due to chronic right-sided heart volume and pressure overload.

**ASD clinical presentation.** Approximately 75% of adult patients with ASD are symptomatic by the fifth decade of life, with dyspnea on exertion and fatigue being the most common presenting symptoms. Small ASDs (<10 mm) may close spontaneously by the age of 10 years. However, small ASDs might present later in life due to decreased left ventricular compliance associated with aging. Adults might also present with atrial tachyarrhythmias, paradoxical embolism, right ventricular failure, platypnea, orthodeoxia, or recurrent pulmonary infections.

Atrial flutter and fibrillation are commonly seen in unrepaired ASD patients. The prevalence of these atrial arrhythmias increases with age and is seen in up to 22% of ASD patients over the age of 50 years. The likely mechanism for these arrhythmias is stretching of the atrium from chronic volume overload.

Similar to a PFO, an ASD has an increased risk of paradoxical embolism, leading to cryptogenic stroke. Although the predominant inter-atrial shunt in ASD is left-to-right, transient elevations in RA pressure can produce reversal of flow and facilitate paradoxical embolism. The incidence of paradoxical embolism is reported as 11% to 14% in ASD patients referred for percutaneous closure (42).

Atrial septal defect is one of the most common congenital heart defects found during pregnancy. Pregnant patients with an unrepaired ASD suffer a higher risk of pre-eclampsia and fetal mortality when compared with the general population. The pregnant woman with an ASD is predisposed to paradoxical embolism due to a hypercoagulable state and enhanced right-to-left shunting from increased plasma volume and decreased peripheral vascular resistance. Although percutaneous closure of an ASD during pregnancy can be accomplished, it is preferable to close large ASDs before pregnancy.

**ASD detection.** Transthoracic echocardiography remains the primary diagnostic modality for the detection of ASD, especially in children. In adults, a TEE can identify the margins of the deficient atrial septum and also assess the bordering structures (i.e., aorta, superior vena cava/inferior vena cava, pulmonary veins, atrioventricular valves, and coronary sinus). Patients with inadequate imaging, questionable ASD diagnosis, or unexplained RV volume overload, warrant further assessment with TEE. Contrast echocardiography with agitated saline has a limited role in the
treatment of secundum ASD, except for large defects (Percutaneous ASD closure has largely replaced surgical ASD closures can be performed as an outpatient procedure. technology has evolved such that most adult secundum ASD was pioneered by King and Mills in 1976 (45), but ASD indications for closure. The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend ASD closure for patients with RA and right ventricular enlargement, regardless of symptoms (Class I) (43). Long-term complications occur in up to 10% of patients with unrepaired ASDs. The age at which an ASD is repaired is the single most important predictor of long-term outcomes. In patients undergoing ASD repair before age 24, long-term survival is similar to age- and sex-matched control subjects. Patients with ASD surgical repairs between ages 25 and 41 had a reduced survival after 27-year follow-up, compared with an age- and sex-matched control group.

The reasons for these survival reductions are not completely understood. Several theories include irreversible damage to the right ventricle, age-related increases in pulmonary hypertension, and a higher incidence of atrial fibrillation leading to increased strokes (44). The incidence of atrial arrhythmias and subsequent strokes does not decrease in patients with ASDs repaired after age 40. Nonetheless, closure in these individuals is warranted, given the modest survival benefits, improvement in symptoms, functional status, and incidence of heart failure.

The ACC/AHA guidelines state that smaller ASDs (a diameter of ≤5 mm) with no evidence of right ventricular enlargement or pulmonary hypertension do not require closure, because they are not considered significant enough to affect the clinical course of these individuals. Smaller ASDs that are associated with paradoxical embolism or orthodeoxia-platypnea can be closed according to guideline recommendations (Class IIA).

The only absolute contraindication for ASD closure pertains to patients with irreversible pulmonary hypertension (pulmonary vascular resistance >8 Woods units) and no evidence of left-to-right shunting (Class III). Therefore, in patients with known pulmonary hypertension, a complete assessment of reversibility should be performed. Patients with a pulmonary artery pressure less than two-thirds systemic pressure, a pulmonary vascular resistance less than two-thirds of systemic resistance, or a positive response to pulmonary vasodilator therapy can be considered for ASD closure.

Percutaneous ASD treatment. Percutaneous closure of an ASD was pioneered by King and Mills in 1976 (45), but technology has evolved such that most adult secundum ASD closures can be performed as an outpatient procedure. Percutaneous ASD closure has largely replaced surgical treatment of secundum ASD, except for large defects (>38 mm diameter), insufficient septal rims, or insufficient LA size to accommodate a device. An adequate septal rim requires 5 mm of septal tissue from the ASD to the superior and inferior vena cava, right upper and lower pulmonary veins, coronary sinus, and mitral/tricuspid valves (46). Although a deficient retro-aortic rim (anterior rim) is not a contraindication to percutaneous device closure, careful consideration and technique is required for successful device placement. With experience, operators have been able to close a range of challenging defects, including defects with deficient posterior rim, superior vena cava rim, and even inferior vena cava rims.

A nonrandomized multicenter trial compared percutaneous closure of secundum ASD with the Amplatzer Septal Occluder (ASO) with surgical closure (47). Percutaneous closure was associated with a significant lower complication rate (7.2% vs. 24%), hospital stay (1.0 vs. 3.4 days), and similar efficacy rates (98.5% vs. 100%). A similar nonrandomized, multicenter trial evaluating the safety and efficacy of the Helex Septal Occluder (HSO) for secundum ASD closure used a surgical arm as the control group (48). The transcatheater Gore-Helex group had less major adverse events at 12 months (5.9% vs. 10.9%) with comparable clinical success rates (a composite endpoint of safety and efficacy of 91.7% vs. 83.7%, p < 0.001 for noninferiority). In addition, percutaneous ASD closure costs less than surgical repair. The current ACC/AHA Congenital Heart Disease guidelines do not differentiate between percutaneous and surgical repair of ASD except for ASDs other than the secundum type. Thus, percutaneous closure of secundum ASD is now the preferred method of repair in those patients with appropriate anatomy.

Percutaneous device options. Although there are 15 devices internationally available for percutaneous secundum ASD closure, there are only 3 FDA-approved devices in the United States. The ASO was the first device approved by the FDA for transcatheter closure of ASD (Fig. 5). Since its approval in 2001, approximately 46,000 have been implanted in the United States, and 200,000 have been implanted worldwide. The ASO device is composed of a braided nitinol wire mesh. It is a self-centering, self-expandable device that is shaped into 2 flat discs with a connecting waist. Polyester fabric inserts are sewn into the nitinol wire mesh to promote tissue growth and defect closure. The ASO device is delivered via a 60- to 80-cm-length sheath that is 6- to 12-F in diameter, depending on the device size. The device size is determined by the waist diameter, which ranges from 4 to 38 mm and corresponds to the atrial defect diameter. Once the device has been placed, it can be easily recaptured into the delivery sheath for re-positioning, as long as the delivery cable has not been released. The ASO has been the most-used percutaneous device for structural heart disease with high success rates and low complication rates.

The Amplatzer Multi-Fenestrated Septal Occluder or “cribriform occluder” is similar to the ASO device with the exception of a narrow waist and equal sized atrial discs. This
The device is designed for use in ASDs with multiple contiguous defects.

The Gore HSO was approved by the FDA in 2007 for percutaneous ASD closure. The HSO is composed of an expanded polytetrafluoroethylene membrane connected by a single nitinol wire (Fig. 6). Once deployed, the HSO device has a double disc shape that straddles the septal defect. The nitinol wire frame forms a locking loop that secures the LA and RA disks to each other, thus sealing the atrial defect. The HSO device is available in diameters ranging from 15 to 35 mm, in 5-mm increments, and requires a 10-F delivery sheath catheter. The HSO device can be repositioned if the locking loop has not been deployed. Once the locking loop has been set, a retrieval cord is available for device removal if necessary. The HSO is soft and flexible and is well-tolerated but not self-centering and is preferable for use in smaller ASDs.

Percutaneous ASD closure complications. Transcatheter ASD closure is a safe procedure with a low complication rate. Several reports reveal a 1.2% to 2.5% major complication rate and 3.4% to 6.1% minor complication rate (47–49). Major complications include device embolization, erosion, pericardial effusion with tamponade, device thrombus, stroke, and endocarditis. Minor complications include excessive inflammatory reactions (perhaps due to nickel allergy), cardiac arrhythmias, and femoral access site complications. The most serious and prevalent complications after percutaneous ASD will be discussed.

ATRIAL ARRHYTHMIAS. The incidence of post-procedural atrial fibrillation is 4.1%, which is higher than with PFO closure (36). This increased incidence of atrial fibrillation in ASD closure might simply be part of the predisposition of patients with ASD to develop atrial fibrillation. Alternatively, a local inflammatory reaction might irritate the atria automatically. Stretching the atrial septum with large devices might also predispose to arrhythmias. Atrial flutter/fibrillation is an important cause of long-term morbidity and mortality in post-closure ASD patients for both surgical and percutaneous repair.

DEVICE EROSION. Although device erosion is a rare complication of percutaneous ASD closure, there was a sharp increase in this complication shortly after the FDA approved the ASO device in 2001. During the FDA trials, devices were implanted that were, on average, 0.5 mm larger than the stretched diameter of a sizing balloon, and there were no reported cases of ASO device erosion. However, post-marketing reports of device erosion sparked a physician review panel that revealed that 68% of patients developed symptoms within 72 h. Device perforation occurred in the LA roof and aorta, RA roof and aorta, and both atria in 1 case (50). Of the 28 cases evaluated, 89% of patients had either a deficient aortic rim and/or deficient superior rim. It was the consensus that an oversized device was the most likely cause of device erosion. Mechanistically, the oversized device rubs against the atrial walls with each cardiac cycle, leading to erosion through the area of contact. The recommendation of this panel was to avoid oversizing by >2 mm beyond the stretched atrial defect diameter (by balloon sizing). After the implementation of this guideline, the incidence of ASO device erosions has decreased.

DEVICE EMBOLIZATION. The reported rate of device embolization ranges from 0.55% to 1.7% (51). Procedural characteristics that increase the rate of device embolization include smaller devices and insufficient septal rims. Embo-
lization is usually apparent during the procedure, but delayed embolizations also occur. Most of these embolized devices are retrievable by percutaneous techniques, which have been described for the ASOs and Gore Helex devices (51,52). Only a minority of embolized devices require surgical removal or subsequent surgical closure of the ASD.

**DEVICE THROMBOSIS.** The incidence of thrombus formation on the device is low and device-dependent. Risk factors for device thrombosis include post-procedure atrial fibrillation, persistent ASA, and coagulation disorders (53). The incidence was approximately 1.2%, with the CardioSEAL/STARRflex having the highest rate (7.1%), whereas the Amplatzer device had no thrombus formation (53). Clinical studies of the Amplatzer and Gore Helex devices reveal an incidence of thrombus formation of 0.2% and 0.8%, respectively (13,53). The treatment for device thrombosis is anticoagulation; however, there is a risk of stroke when the thrombus is on the LA side, and surgical treatment might be required for large, mobile thrombi.

**Conclusions**

There have been impressive advances over the past 20 years in the field of percutaneous repair of atrial defects. Percutaneous ASD closure is relatively safe, reduces clinical sequelae associated with ASD, and has become the preferred method for treatment of secundum ASDs. Percutaneous PFO closure is also a safe procedure that is performed on an “off-label” basis. There are strong observational data to suggest benefit from PFO closure in conditions such as cryptogenic stroke, migraine headache with aura, decompression illness, and platypnea-orthodeoxia syndrome. The recent randomized trial data on PFO closure for migraine and cryptogenic stroke have contradicted the observational reports, but these results might be due to the particular device that was used, which no longer is being produced. The results of the current randomized trials for secondary stroke prevention and treatment of severe disabling migraine are eagerly awaited and might clarify the role of percutaneous PFO closure.

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**Reprint requests and correspondence:** Dr. Jonathan Tobis, University of California–Los Angeles, Interventional Cardiology, 10833 Le Conte Avenue, Factor B976, Los Angeles, California 90095. E-mail: jtobis@mednet.ucla.edu.

**REFERENCES**


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APPENDIX

For supplementary references and videos, please see the online version of this article.