When and how to fix a ‘hole in the heart’: Approach to ASD and PFO

**ABSTRACT**

Abnormalities in the atrial septum range in severity from patent foramen ovale (PFO), a residual cardiac structure found in approximately 25% of the general population, to uncommon, complex lesions associated with significant shunt flow and heart enlargement. While correcting some of these abnormalities is beneficial, most other defects warrant correction only under very specific circumstances.

**KEY POINTS**

- Any patient with a large atrial septal defect (ASD) and otherwise unexplained right heart enlargement should be considered for correction of the ASD.
- Percutaneous closure is now the standard of care for most secundum ASDs. Candidates must have normal pulmonary venous return and, preferably, only one ASD.
- Significant pulmonary hypertension should be carefully evaluated before closure of an ASD is attempted.
- PFO is more common in patients with cryptogenic stroke than in matched controls. The combination of a PFO and an atrial septal aneurysm may significantly boost the risk of recurrent stroke.
- The ideal antiplatelet or antithrombotic therapy for stroke patients with PFO remains uncertain.
- Until very recently, percutaneous closure of a PFO was approved only through a humanitarian device exemption for patients with recurrent stroke receiving anticoagulation.

Two high-profile cases have recently brought “holes in the heart” to public attention. The first involved a professional athlete (Tedy Bruschi of the New England Patriots) who suffered a stroke only days after finishing his season. He eventually had his defect corrected and returned to athletic competition. The other involved a major political figure (Israeli Prime Minister Ariel Sharon) who suffered a second, significantly larger stroke only days before his defect was scheduled to be corrected.

In both cases, detailed descriptions of the patient’s cardiovascular anatomy were published in the lay press, but unfortunately the descriptive terminology was often misleading. This is not surprising, as even many physicians confuse the terminology of septal defects. These semantics are important, as the therapeutic approach to patients with abnormalities of the atrial septum differs according to the anatomical findings and clinical circumstances that brought the abnormality to attention.

**ASD AND PFO: WHAT IS THE DIFFERENCE?**

The first pathologic description of an abnormality in the atrial septum was made in 1513 by Leonardo da Vinci, who wrote: “I have found from a, left auricle, to b, right auricle, the perforating channel from a to b.”

To best understand the various abnormalities in the atrial septum, it is essential to
review its embryologic development (FIGURE 1). We all start out with a single atrium. Then, the septum primum starts growing downward from the roof of this chamber and divides it into a left and a right side. Fenestrations eventually form in the middle of the septum primum, creating the ostium secundum. A second septum (the septum secundum) then develops on the right atrial side of the septum primum. More than 99% of the time this septum will completely cover the opening of the septum primum. If it fails to properly develop, however, the result is a secundum atrial septal defect (secundum ASD), a hole in the septum that permits blood to flow in either direction (left to right or right to left), depending on the atrial pressures.

Even after normal formation of the septum secundum, an opening—the foramen ovale—remains between the septa after all cardiac development is completed. Functioning as a one-way (right-to-left) valve, this opening provides a way for blood to bypass the lungs in utero. At birth, lung pressures drop and the blood pressure in the left atrium exceeds that of the right atrium. This change in pressure leads to apposition of the septum and complete sealing of the defect within hours of birth in up to 75% of infants. If this final step does not occur, a patent foramen ovale (PFO) remains.

More complicated defects of the septum include the sinus venosus ASD, which forms at the junction of the superior or inferior vena cava and the right atrium. This type of defect is commonly associated with abnormalities in blood return from the lungs (anomalous pulmonary venous return).

Even rarer are the primum ASDs or atrioventricular canal defects, which also involve the atrioventricular (mitral and tricuspid) valves. These are commonly seen in patients with trisomy 21 (Down syndrome), and frequently present early in life due to their significant impact on cardiovascular physiology. For the sake of brevity, sinus venosus ASD, primum ASD, and the extremely rare coronary sinus ASD will not be further discussed in this paper.

One other notable septal abnormality occurs when there is overabundant and weakened tissue in the septum primum, making the septum very floppy. In general, if the maximal excursion is at least 15 mm (measured from the left atrium to the right atrium by echocardiography), this abnormality is called an atrial septal aneurysm. If the maximal excursion is less than 15 mm, it is then referred to as a “redundant atrial septum.” The definitions, however, vary throughout the literature and no true “gold standard” exists.

Occasionally, a secundum ASD coexists in patients with an atrial septal aneurysm, though a PFO is more likely to be present. In some series, as many as 60% of patients with PFO have a concomitant atrial septal aneurysm.

**Echo studies reveal the difference between ASD and PFO**

It is usually easy to differentiate ASD from PFO if the interatrial septum can be adequately imaged, typically with tranesophageal echocardiography. During this procedure, the patient is sedated and an imaging probe is passed through the mouth into the esophagus.

Other evidence that supports the diagnosis of ASD includes electrocardiographic changes such as the classic RSR′ pattern of an incomplete right bundle branch block, occasionally accompanied by right axis deviation.

If the patient does not have severe pulmonary hypertension, blood flows through the ASD from left to right during most of the cardiac cycle. On the other hand, blood flows through a PFO only from right to left, and only during the brief phases of the cardiac cycle when the right atrial pressure exceeds the left atrial pressure or following straining. This difference can readily be seen on color Doppler imaging (FIGURE 2).

Occasionally, in patients with PFO, the atrial septum can become stretched due to significant atrial enlargement, as in severe pulmonary hypertension. In such circumstances the overlap between septa is reduced, and left-to-right shunting can also occur (FIGURE 3).

**WHEN TO SUSPECT ASD**

Secundum ASD is the third most common congenital heart defect in adults, after mitral valve prolapse and bicuspid aortic valve.

Secundum ASD is often mistaken for other abnormalities or overlooked, as its symptoms (typically fatigue and breathlessness) can be
Holes in the heart: two main types

The normal atrial septum consists of two layers, the septum primum and the septum secundum.

The septum primum forms first, but leaves a window, the ostium secundum. The septum secundum forms later, and usually covers the ostium secundum.

In utero, the foramen ovale allows blood to flow from the right atrium to the left, bypassing the lung. But in up to 25% of people this one-way flap fails to close after birth.

If the septum secundum fails to cover the ostium secundum, blood can flow in either direction through the resulting atrial septal defect (ASD), although the direction is mostly from the higher-pressure left side to the lower-pressure right side during most of the cardiac cycle.
subtle and nonspecific. Physical findings, such as a fixed split second heart sound (due to loss of differential effects on right-sided and left-sided filling pressures from the drop in intrathoracic pressure that normally occurs during inspiration) and a pulmonic outflow murmur (the result of increased pulmonary blood volume from shunting), are also often overlooked. ASD should be suspected whenever the right heart is found to be enlarged and there is no other good explanation for it. Occasionally, patients present late in life with ASD-related symptoms when the left atrial pressure rises because of a stiff left ventricle and diastolic dysfunction (often the result of long-standing hypertension or coronary artery disease). Correction of these defects has recently been shown to be safe and to result in reduction in right heart size.11

The flow of blood through the defect (shunt) is determined by the size of the defect and the compliance of the ventricles. The greater the left-to-right blood flow, the greater the risk of long-term complications such as atrial fibrillation and pulmonary hypertension. The latter condition affects up to 20% of adults with ASD and, if uncorrected, may eventually result in Eisenmenger syndrome.

In Eisenmenger syndrome, the right atrial pressure exceeds the left atrial pressure and the shunt is reversed (right to left), resulting in systemic hypoxia.12 The telltale sign of a right-to-left shunt is that oxygen saturation does not increase when oxygen is given. Multiple complications eventually ensue, and the condition has generally been considered irreversible. A recent report, however, describes a patient with Eisenmenger syndrome whose pulmonary pressures declined with prolonged infusion of prostacyclin and who was able to have the causative ASD successfully repaired.13

Another condition associated with ASD is stroke, which presumably results from paradoxical embolization (blood clots forming in the extremities and reaching the cerebral circulation by passing through the ASD). This association is further described in the section on PFO and stroke, below.

When Should an ASD Be Fixed?

The traditional measure used to determine whether an ASD should be corrected is the degree of shunting, which can be estimated using echocardiography or magnetic resonance imaging or directly measured by obtaining serial oxygen saturations in the heart chambers during catheterization.

A high Qp/Qs ratio. The ratio of pulmonary blood flow (Qp) to systemic blood flow (Qs) can be calculated as:
(aortic saturation – mixed venous saturation) / (pulmonary vein saturation – pulmonary artery saturation),

where the mixed venous saturation is calculated by multiplying the superior vena cava saturation by 3, adding the inferior vena cava saturation, and dividing this sum by 4. The pulmonary vein saturation can be assumed to be 95% if not directly measured.

The recommendation has been to close the defect if the pulmonary blood flow is at least 50% greater than the systemic blood flow (Qp/Qs ≥ 1.5). However, although this requirement makes perfect sense in children or young adults, a Qp/Qs cutoff of 1.5 could miss important defects in older adults who could otherwise benefit from repair. In particular, shunts known to be brisk in early life can decrease over time, particularly if the pulmonary vasculature becomes progressively more diseased (less compliant) and the right heart pressure increases (pulmonary hypertension, likely the predecessor of Eisenmenger syndrome).

Right heart enlargement that is not otherwise explainable is probably the best indicator of a significant shunt. Enlargement can best be assessed using standard transthoracic echocardiography, which can also be used to noninvasively assess the pulmonary pressures (by measuring the velocity of tricuspid regurgitation) and to detect any associated structures such as an atrial septal aneurysm.

Is repair feasible? In patients with advanced pulmonary hypertension, it is important to ensure that repairing the defect remains feasible and will not lead to harm. In some patients with pulmonary hypertension resulting in right-to-left flow, the ASD may be serving as a relief valve, and repairing it could result in further elevation in pulmonary pressures and a drop in left heart output, with disastrous complications. Whether repair is feasible can be further assessed by pulmonary vasodilator testing to determine if lung pressures can be readily reduced. This procedure is usually performed under careful observation in the cardiac catheterization laboratory.

Another technique is to transiently occlude the defect with a balloon and examine the effect on systemic and pulmonary artery pressures as well as on oxygen saturations. If lung pressures remain stable or are reduced and the systemic pressures and cardiac output are maintained, repair of the defect is likely possible.

Candidates for percutaneous closure of ASDs should also have:

- Only one defect (or possibly a few). Multiple defects are present in up to 17% of cases.14
- A defect smaller than about 4 cm.
- Pulmonary veins that drain back normally to the left heart. An anomalous pulmonary vein or veins is present in about 10% of patients15 and should be surgically corrected.

Secundum ASD is often mistaken for other abnormalities or overlooked.
• Septal rims that are wide enough to hold the occlusion device (at least 4 mm around).

Transesophageal echocardiography is the best test for making these assessments.

WHAT SHOULD BE DONE ABOUT AN INCIDENTALLY DISCOVERED PFO?

The pathological importance of PFO is not clear. The prevalence of PFO may decrease as patients get older, perhaps implying that patients with PFO tend to die young. However, another explanation is that some PFOs may spontaneously close over time.

What to do when a PFO is found during routine clinical imaging remains unclear. In a recent study, healthy volunteers underwent transesophageal echocardiography and were subsequently followed for a median of 5 years. Those found to have PFO had no increased risk of stroke in this interval. Furthermore, no clinical studies have established the benefit of any primary preventive measures in patients with PFO. Nevertheless, a recent survey found that thoracic surgeons strongly favored closing an incidentally discovered PFO during surgery, in most cases regardless of whether the patient had suffered any previous medical sequelae and even at the cost of dramatically altering the surgical procedure.

The first report of a medical consequence related to PFO was in 1877, when Cohnheim described a young woman with an embolic stroke. Since that time, associations have been drawn between PFO and migraine headaches, decompression sickness, platypnea orthodeoxia (a condition associated with shortness of breath in which systemic levels of oxygen drop on sitting or standing after a recumbent position), and left-sided valvular heart involvement with carcinoid tumor. Of these, the association is strongest between PFO and stroke.

THE LINK BETWEEN PFO AND STROKE

Much of the evidence supporting a link between PFO and stroke comes from a series of comparisons of patients with unexplained (cryptogenic) stroke and healthy controls. A meta-analysis of these data found PFO to be three times more common in patients with cryptogenic stroke than in age-matched and sex-matched controls.

Association does not prove causation, however. Granted, occasional cases have been reported in which serpiginous (snake-like) thrombi that looked like vein casts were found trapped within the PFO (the so-called embolus in transit), which would seem to be the smoking gun linking PFO to stroke. However, how often such a mechanism is involved remains uncertain. The frequency of deep venous thrombosis in patients with cryptogenic stroke and PFO ranged from only 10% in one series to up to 57% in another. (The number may be higher: some thromboemboli may come from the pelvic veins, where they would not be detected unless the patient underwent magnetic resonance venography, which is not universally available.) Moreover, hypercoagulable states are rarely discovered in patients with PFO and cryptogenic stroke.

Once a patient with PFO has a presumed embolic event, a number of factors appear to increase the risk of future strokes. These include the coexistence of an atrial septal aneurysm. In the same meta-analysis noted above, concurrent PFO and atrial septal aneurysm was six times more common in patients with stroke than in age-matched and sex-matched controls. Furthermore, two recent studies found no increase in the risk of future stroke in PFO patients unless an atrial septal aneurysm was also present. Characteristics of the PFO itself that may increase stroke risk include a wide (≥4-mm) anatomic separation between the septum primum and septum secundum, larger degrees of right-to-left shunting, and shunting at rest (without provocation).

EVALUATION OF PATIENTS WITH CRYPTOGENIC STROKE

A cryptogenic stroke by definition eludes diagnosis by the standard diagnostic evaluation, which usually includes extensive cerebrovascular imaging. PFO should most be suspected in younger patients, in whom cryptogenic stroke accounts for up to 40% of strokes. More than 50% of stroke patients younger than 45 years have a PFO.

The “bubble study” is an easy and sensi-
tive test for a PFO or ASD. Agitated saline is injected intravenously while the patient performs the Valsalva maneuver. If bubbles can be seen on transthoracic echocardiography in the left atrium or ventricle within three cardiac beats after injection, a right-to-left communication is present (FIGURE 4). Some limitations of this technique are that it can be done only in cooperative patients, and the images may be technically inadequate (most often in patients who are obese, have chronic lung disease, are mechanically ventilated, or cannot roll onto their side for examination).32

An alternative way to detect the passage of microbubbles across the septum is to listen for them entering the cerebral circulation with transcranial Doppler ultrasonography. This is feasible even if echo images are not obtainable and may be the most accurate method of shunt detection.33

Transesophageal echocardiography should ideally follow either of these studies to further evaluate the septum.34 This can help to differentiate a PFO from a secundum ASD (as noted above), both of which can result in right-to-left shunting during the Valsalva maneuver. Transesophageal echocardiography can also assess for other sources of emboli, including atheromatous debris from the aortic arch, left atrial appendage thrombus from atrial arrhythmia, left ventricular thrombus from previous myocardial infarction, and cardiac tumors such as myxoma or papillary fibroelastoma.35

■ OPTIMAL THERAPY IS UNCERTAIN IN PATIENTS WITH STROKE AND PFO

After completing the workup of the stroke patient and deciding that a PFO was involved with the event, the clinician is faced with the daunting decision of which therapy to give.

Anticoagulant therapy
Under most circumstances, the PFO was only the conduit through which a thrombus or platelet plug supposedly passed into the arterial circulation. The physician must therefore also account for the predilection for the formation of a thrombus or platelet plug.

Some of the options to prevent future blood clots include aspirin, a thienopyridine such as clopidogrel (Plavix), aspirin and a thienopyridine together, and warfarin (Coumadin).

To date, no prospective trial has addressed the anticoagulation issue specifically in patients with presumed paradoxical embolization.

In the Warfarin-Aspirin Recurrent Stroke Study (WARSS),36 2,206 patients with prior stroke were randomized to receive aspirin (325 mg/day) or warfarin (target international normalized ratio 1.4–2.8). After 2 years, the incidence of recurrent stroke or death was similar in both groups.

In a substudy of WARRS called PICCS (Patent Foramen Ovale in Cryptogenic Stroke Study),37 250 patients with cryptogenic stroke underwent transesophageal echocardiography, which revealed PFO in 98 (39%). The risk of subsequent stroke or death did not appear to be higher in patients with PFO than in patients without PFO, although the use of medical therapy in the entire population may have lessened the impact of PFO.
Of note, in the patients with PFO, the 2-year risk of stroke or death was 17.9% with aspirin therapy and 9.5% with warfarin, though this difference was not statistically significant.

In fact, most studies comparing warfarin and antiplatelet therapy have either shown neutral results or favored warfarin in reducing cerebrovascular events, albeit with an increased risk of bleeding. A meta-analysis\(^38\) that included the PICCS data reported the annual rate of stroke or death was 4.7% in patients with cryptogenic stroke and PFO taking warfarin and 8.9% in those taking aspirin, although the difference was not statistically significant (relative risk= 0.53, 95% confidence interval 0.18–1.58).

Although warfarin is not clearly superior, it is often recommended as first-line therapy in patients with stroke resulting from presumed paradoxical embolization. Aspirin with or without a thienopyridine may be a reasonable alternative for patients who cannot take warfarin.

**Closure of the PFO**

The other clinical option to consider is to close the PFO, either surgically or percutaneously. Though surgery can usually be performed with an extremely low risk of death, it is still associated with significant complications from the median sternotomy.

Contraindications to percutaneous closure include another evident source of cardioembolic stroke (such as a known carotid stenosis or a left atrial appendage thrombus); severe pulmonary hypertension or elevated pulmonary vascular resistance; recent gastrointestinal bleeding; other congenital heart defects that cannot be repaired concurrently without surgery; a venous thrombus or vena cava filter that interrupts the passage of a catheter from the access site to the foramen; a known hypersensitivity or contraindication to antiplatelet or anticoagulant therapy; and infection or unexplained fever at the time of implantation.

No randomized clinical trial data are available to properly assess the safety or benefit of percutaneous PFO closure in patients with a first-time or recurrent stroke. Retrospective and prospective cohort studies, however, have suggested a slightly lower recurrence rate of transient ischemic attack or stroke after closure than with medical therapy, though these data remain controversial.\(^20,39–42\) A systematic review of these trials in 2003 suggested a slight benefit to percutaneous closure over medical therapy in secondary prevention,\(^43\) but stressed that randomized trials need to be performed to evaluate this more fully.

Until recently, two different occlusion devices (see below) were available through a humanitarian device exemption (HDE) from the US Food and Drug Administration (FDA) to correct PFOs in patients with recurrent presumed embolic strokes for whom anticoagulation therapy had failed.\(^44\) An important criterion for granting an HDE is that the target population for use of the device be no more than 4,000 patients yearly. After further review, the FDA decided that this criterion was no longer being met, and on August 14, 2006, both manufacturers decided to voluntarily withdraw their HDEs.\(^45\) Each company is currently making its devices available to patients with recurrent cryptogenic strokes presumed to be due to paradoxical embolism through a PFO, for whom conventional medical therapy has failed and who are willing to be enrolled in a registry.

Percutaneous occlusion of PFO for a first-time stroke presumed to be PFO-related is not currently recommended, and there are few data suggesting clinical benefit in this patient subset. Because the long-term safety of closure devices is unknown, we do not know whether the benefits truly outweigh the risks. Two large randomized clinical trials, the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) with the Amplatzer PFO occluder (AGA Medical; Golden Valley, MN) and the Evaluation of the STARFlex Septal Closure System in Patients with a Stroke or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a PFO (CLOSURE 1) with the STARFlex occluder (NMT Medical; Boston, MA) are currently comparing anticoagulation or antiplatelet therapy and device closure in patients with first-time cryptogenic stroke. Both of these studies have reported difficulty in enrolling patients, presumably due to preconceived notions on the part of patients.
and physicians that one treatment strategy may actually be preferable.

**HOW DO THE DEVICES WORK?**

Percutaneous occlusion of septal defects in human beings was first attempted in the 1970s, and devices have been slowly perfected over time. Today’s devices are compact, self-expanding, tremendously durable, and compatible with magnetic resonance imaging magnets.

The Amplatzer septal occluder (AGA Medical; Golden Valley, MN) achieved full FDA approval for ASD closure in December 2001, and the Gore Helex septal occluder (WL Fore & Associates; Flagstaff, AZ) was approved in August 2006. For PFO closure, adequately trained physicians can choose between the CardioSeal (NMT Medical; Boston, MA) and the Amplatzer PFO occluder (FIGURE 5).

All these devices have a proven record of safety, though each appears to have unique concerns. Amplatzers, particularly larger ones implanted at a shorter distance from the aorta, may be associated with a future risk of device erosion, which can have catastrophic consequences. The CardioSeal, on the other hand, appears to pose a slightly higher risk of thrombosis, though the implications of either of these problems remain uncertain.

**Implanting the device**

The device is usually implanted on the day of admission, with subsequent overnight observation to watch for local bleeding.

Although both fluoroscopy and transesophageal echocardiography have traditionally been used to guide the implantation, the use of intracardiac echocardiography during percutaneous closure has been a substantial advance and precludes the need for general anesthesia. For the patient, the experience is often not different from that of a diagnostic catheterization.

After venous access is obtained, a right heart catheterization is typically performed in ASD cases to measure the right heart pressures and to assess the degree of shunting by measuring the oxygen saturations. With PFO this step is often not necessary.

**FIGURE 5.** The two available devices that have been approved for percutaneous closure of patent foramen ovale (PFO) through a humanitarian device exemption. Left, the Amplatzer PFO occluder (AGA Medical; Golden Valley, MN); right, the CardioSeal occluder (NMT Medical; Boston, MA).

The echocardiographic probe is then inserted using ultrasonographic and fluoroscopic guidance, and the interatrial septum is imaged. The defect is crossed using a curved catheter and semistiff wire.

A soft, pliable balloon is then inserted to measure the defect. For ASDs this step is essential, as the device size is selected according to the measured “waist” of the defect. For PFOs the tunnel length is probably more important than the degree of stretched separation between the septa to ensure that the device properly “sandwiches” the defect and therefore prevents residual shunting.

The occluder is then carefully released under fluoroscopic and intracardiac echocardiographic guidance.

The procedure usually takes less than an hour, and the patient can be discharged the next morning with the same postprocedural limitations as after a diagnostic heart catheterization.

In a recent prospective study, participating centers had the option of referring ASD patients for percutaneous occlusion with an Amplatzer device or surgical repair. Occlusion was successful in 96% of percutaneous procedures and in 100% of surgeries ($P = .006$). No patient died in either group; complications occurred in 7.2% of patients in the device group and 24.0% of patients in the surgical group ($P < .001$). The mean length of hospital stay was 3.4 ± 1.2 days in the surgical group and 1.0 ± 0.3 days in the device group.
ATRIAL SEPTAL ABNORMALITIES

Reported adverse outcomes with percutaneous occlusion include device embolization, device thrombosis, mitral regurgitation, and pulmonary vein obstruction. In most series the risk of such complications was between 1% and 3%.50

The anticoagulation regimen after device closure is controversial. Patients at most centers get aspirin and a thienopyridine for at least 6 months, after which the device should be completely endothelialized.

Patients should also receive endocarditis prophylaxis for at least the same duration of time and possibly for life after percutaneous closure, although this practice is unsubstantiated.

Following percutaneous closure of ASD, right heart hemodynamics can improve quite dramatically.51 Right heart enlargement typically regresses over weeks to months, and pulmonary artery pressure may also diminish somewhat.

Follow-up after percutaneous repair of septal anomalies

The device manufacturers recommend that patients undergo follow-up transthoracic echocardiography, typically performed within the first 3 months, at 6 months, and at 1 year after implantation of an occluder. Recent data suggest a possible role for screening transesophageal echocardiography at around 3 months after the procedure to exclude device-related thrombosis.

Because the long-term effects are unclear, patients should have a yearly follow-up visit with a cardiologist familiar with occluders, and possibly echocardiography on a yearly basis as well. If the device is repeatedly shown to be stable, this interval may be extended to every 3 years, providing the patient remains asymptomatic.

Of importance: patients with a repaired ASD still face an increased risk of developing atrial fibrillation that directly correlates with the age at which the defect is corrected (later correction = higher risk).52 Evidence of new atrial fibrillation, symptoms suggestive of a stroke or transient ischemic attack, progressive right heart enlargement, or the development of pulmonary hypertension in a patient with a repaired ASD should prompt an echocardiographic evaluation (ideally transesophageal) to confirm that the device or patch is stable. Similarly, in a patient with a repaired PFO, residual shunting and device thrombosis should be excluded if a new stroke or transient ischemic attack is suspected.

REFERENCES


