# Contemporary Management of Patent Foramen Ovale

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In 1877, Cohnheim performed a necropsy on a young woman who had died from a stroke. He hypothesized that a clot passing through the patent foramen ovale must have caused her demise.[1] Thus, the first description in medical literature on paradoxical embolism appeared.

The foramen ovale is a pivotal feature during intrauterine life. As depicted in Figure 1, the interatrial septum primum on the left side and the interatrial septum secundum on the right side maintain a central hole after having grown from the periphery to the center. This hole is positioned caudally in the septum secundum and cranially in the septum primum, forming a slit valve that opens with pressure from the right. The blood from the umbilical vein entering through the inferior vena cava from the bottom of the right atrium keeps this door open until after birth. From then on, the left atrial pressure, slightly higher than the right atrial pressure, keeps the valve shut. In most individuals, the caudal portion of the septum primum on the left side and the cranial portion of the septum secundum on the right side fuse permanently, closing the foramen. In a minority of the population, however, the fusion does not take place and the foramen remains able to be opened (patent).

## Prevalence of Patent Foramen Ovale

A pooled analysis of autopsy studies yielded an average prevalence of patent foramen ovale (PFO) of 26% (range 17% to 35%) (Table).[2]

In most echocardiographic studies on ischemic stroke patients, the prevalence of a PFO is higher in patients with a cryptogenic stroke. In a recent study of 61 patients, a PFO was found in 45% of those with cryptogenic stroke and in 23% of those with a stroke associated with large vessel atherosclerosis, lacunar ischemia, or cardiogenic embolism.[3] This discrepancy is larger in young patients than in the elderly. Whereas the absolute risk of cryptogenic (including paradoxical) strokes increases with age, the relative stroke risk of a PFO is reduced as other etiologies become more dominant (Table).[2] Some studies focusing on elderly populations have thus failed to reveal a relationship between PFO and stroke.

## Clinical Problems Attributed to PFO

### *Paradoxical Embolism*

Although large thrombi may occasionally pass through the foramen ovale (Figure 2), this is more common for small clots of a few millimeters that would normally embolize to the lungs and spontaneously lyze in the lung filter without clinical sequelae. These clots will be clinically recognized only if they paradoxically embolize to a sensitive organ such as the brain, the eye, or the heart muscle via the coronary arteries. The source of the clots cannot be established in most patients; fewer than 10% will have deep-vein thrombosis apparent on phlebography.[4] Although most emboli presumably arise from systemic veins, the PFO itself has been suspected to be a source of thrombus because of stagnated blood in the tunnel. However, the fact that, to our knowledge, dislodging of such thrombi has not been reported during transcatheter PFO closures argues against this hypothesis.

The percentage of cryptogenic strokes among ischemic strokes (about 75% of all strokes) varies from 8% to 44%, with a mean of 31% (Table).[2] Assuming an annual incidence of 750 000 strokes in the United States,[5] about 600 000 will be ischemic. Of these, about 200 000 will be cryptogenic, and of these roughly 70 000 will be associated with a PFO. By adding patients with transient ischemic attacks (TIA) or peripheral embolism, paradoxical embolism associated with a PFO identifies about 100 000 patients per year in the United States for whom

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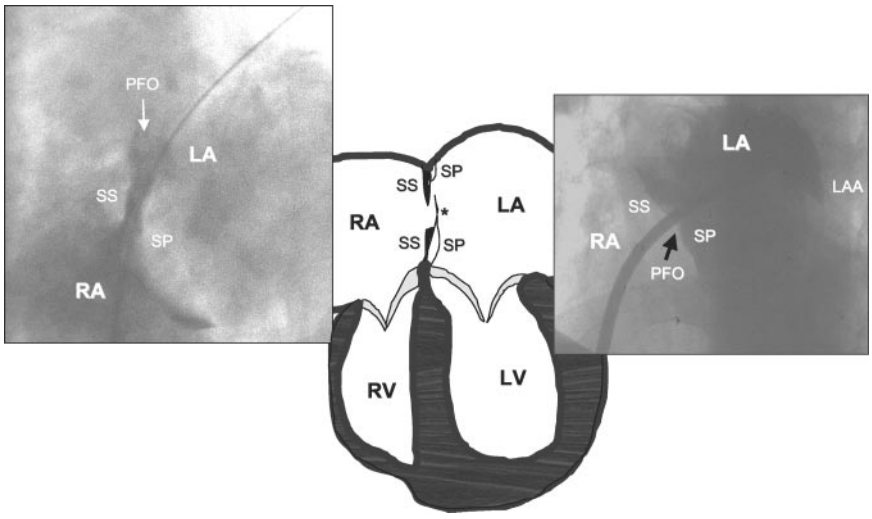


**Figure 1.** Center, Frontal aspect of the heart of an individual with a patent foramen ovale. The caudal portion of the interatrial septum is primarily formed by the septum primum (white) on the left side. At the base, it is reinforced by a remnant of the septum secundum (black) on the right side. The caudal portion of the septum primum (*) is thin and occasionally shows aneurysmatic hypermobility (atrial septal aneurysm). The cranial part of the interatrial septum is primarily formed by the septum secundum on the right side, with a remnant of the septum primum close to the roof of the left atrium. Flow or pressure from the right side (particularly from the lower part of the right atrium) opens and flow or pressure from the left side closes the patent foramen ovale. Left, Right atrial contrast medium injection with a guidewire across the foramen ovale. The transit of the contrast material through the unusually long, tunnel-shaped foramen is indicated by an arrow. Right, Contrast medium injection into the left atrium via a catheter passed through the patent foramen ovale. There is no shunt at the patent foramen ovale (arrow) as the valve mechanism functions even with the catheter across it. LA indicates left atrium; LAA, left atrial appendage; LV, left ventricle; PFO, patent foramen ovale; RA, right atrium; RV, right ventricle; SP, septum primum; and SS, septum secundum.

closure of a PFO becomes an option. That amounts to roughly 10% of the yearly number of patients undergoing coronary angioplasty in the United States. Add to these the clinical syndromes discussed below, and the scope of PFO as a clinical problem can be grasped.

### *Decompression Illness in Divers*

An increased prevalence of brain lesions has been found in divers even in the absence of recognized decompression illness.[6] In a seminal study, transcranial Doppler ultrasonography detected a right-to-left shunt in all divers with multiple brain lesions.[7] A foramen ovale no doubt accounted for most of these cases. A comparative investigation regarding brain lesions and the presence of a foramen ovale in sport divers and non-diving controls showed that brain lesions were more common in individuals with a foramen ovale, although divers had more brain lesions than non-divers, irrespective of the presence of a PFO.[8] This has led some diving schools to recommend screening for the presence of a PFO for professional divers or avid amateurs. In such divers, PFO closure would make sense.

**Findings of Clinical Studies of PFO**

| | |
|---|---|
| Prevalence of PFO at autopsy | 26 |
| Prevalence of PFO in patients with ischemic stroke | |
| Age <55 years | |
| Cryptogenic | 46 |
| Other | 11 |
| Age >55 years | |
| Cryptogenic | 21 |
| Other | 15 |
| Cryptogenic origin of ischemic stroke | 31 |

Values are given as percentages.

### *Migraine*

The surprising results of a retrospective study in 37 patients with percutaneous PFO closure for diving accidents or paradoxical embolism revived interest about the association between migraine and PFO.[9] Subsequently, 2 recent studies reported a 2- to 5-fold increased prevalence for migraine in PFO carriers.[10,11] The reason for this apparent association between PFO and migraine remains undefined. Small emboli or serotonin not metabolized in the lung were considered as possible causes.

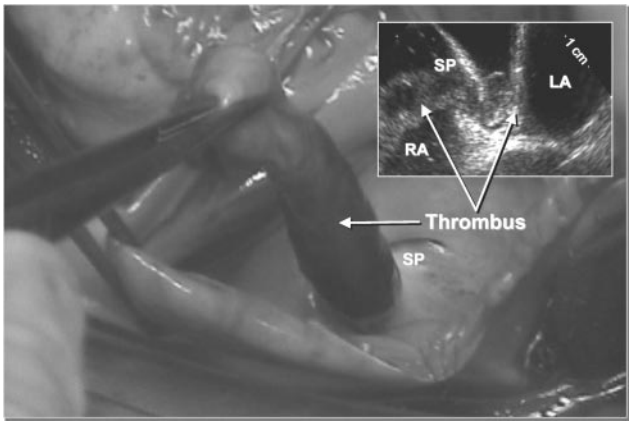


**Figure 2.** A 30-cm long thrombus detected at echocardiography (insert) in a 45-year-old man suffering from pulmonary embolism caused by a fragment breaking off from the tail of the thrombus while it was lodged at its waist in the foramen. The view is from the right atrium. LA indicates left atrium; RA, right atrium; and SP, septum primum

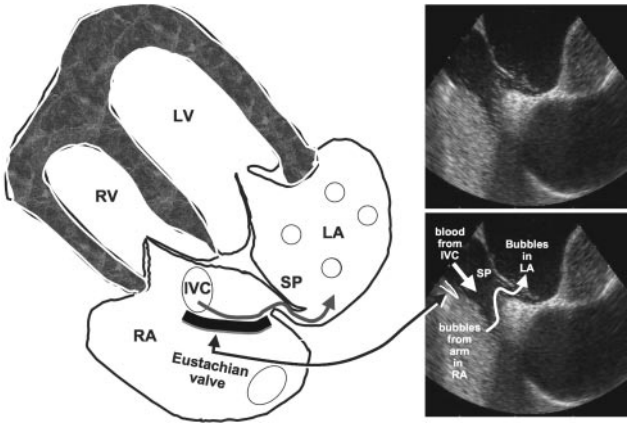


**Figure 3.** Eustachian valve guiding the blood from the inferior vena cava (IVC) directly onto the foramen, thereby pushing open the septum primum (SP) despite the absence of elevated right atrial (RA) pressure. This leads to an increased risk of paradoxical embolism and sometimes to arterial desaturation and cyanosis. On the right side, a TEE is shown with a bubble injection through the arm. The main blood flow from the inferior vena cava is guided along the SP, thereby opening the PFO. Only a few bubbles from the arm manage to pass through the PFO, whereas blood from the IVC, guided by the Eustachian valve, passes freely. Hence, the sensitivity and specificity of a bubble test can be improved by injecting the bubbles into a vein of a lower extremity. LA indicates left atrium; LV, left ventricle; and RV, right ventricle.

### *Miscellaneous*

The risk of a PFO in the perioperative period has not been investigated systematically. However, the increased presence of potential paradoxical emboli (air, venous clots, or fat), in association with unphysiological intrathoracic pressures (ventilation, open chest, straining, etc), is of concern. It has been suggested that high-risk patients be screened for PFO before susceptible surgery.[12]

In the context of pulmonary embolism, a 5-fold increased risk for mortality or systemic emboli was found in patients with a PFO.[13]

A rare and peculiar syndrome is platypnea orthodeoxia.[14] It can be seen in elderly patients who become cyanotic and dyspneic while sitting up; these problems disappear when the patients are lying down. A right-to-left atrial shunt can be documented even in the absence of an elevated pressure in the right atrium. It is assumed that with aging a prominent Eustachian valve becomes redirected to the foramen ovale. Figure 3 explains this mechanism. This may be caused by general enlargement of the heart chambers and the aortic root or by a positional change of the entire heart due to obesity or spinal shortening. Associated pulmonary hypertension may lead to continuous arterial desaturation and cyanosis, irrespective of the patient's upright or supine position.

## Diagnosis of PFO

Although the PFO can occasionally be convincingly documented even in adults with a transthoracic echocardiogram (TTE) (Figure 4), such a diagnosis is rarely unequivocal. Transesophageal echocardiography (TEE), rather than TTE, is the method of choice.[15,16] A bubble test with an aerated colloid solution at the end of a sustained Valsalva maneuver (gush of blood filling the right atrium of the empty heart several beats before the left atrium gets filled, thereby opening the foramen) results in an excellent sensitivity provided that the correct plane is visualized. Transcranial Doppler examination is also very sensitive and specific.[17] Likewise, indicator dilution and pulse oximetry techniques have been validated and found to have a sensitivity of 85% and 76%, respectively, whereas both have a specificity of 100%.[18] None of these latter examinations can distinguish between a shunt at the level of the PFO or elsewhere, however, nor do they give information on the presence or absence of an atrial septal aneurysm (Figure 5).

An atrial septal aneurysm (more appropriately called hypermobile or floppy septum primum) (Figure 5) was initially considered to be an independent risk factor for systemic embolism. Gradually it has been recognized as an accomplice of the PFO rather than a lone culprit. An atrial septal aneurysm without a PFO showed no risk for cryptogenic stroke in a TEE study of about 600 patients with cryptogenic stroke followed-up for 4 years.[15]

## Rationale for PFO Closure in Stroke Patients

Studies on annual recurrences after a cerebral vascular accident (CVA) or a TIA[19–24] reported an incidence ranging from 3%[23] to 16%.[24] In a large study, the recurrent stroke rate or mortality from an embolic event was 6% to 8% per year.[22] A pooled analysis suggests

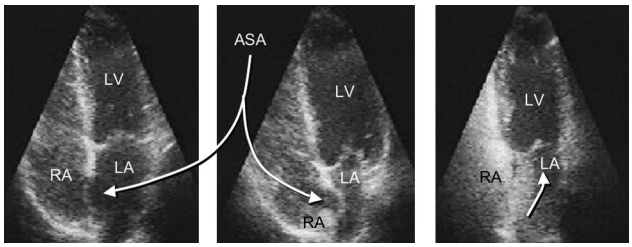


**Figure 4.** Documentation of a PFO and an atrial septal aneurysm (ASA) by TTE. The floppy part of the septum primum undulates between the right atrium (RA, left) and the left atrium (LA, center). The bubble test shows bubbles passing into the LA toward the left ventricle (LV). It is important to make sure that the bubbles cross through the PFO and not through pulmonary shunts. Bubbles crossing through pulmonary shunts appear usually late (after several heart beats) in the LA, irrespective of the Valsalva maneuver. They emerge from anywhere in the left atrium and are usually devoid of the larger bubbles seen in the right atrium.

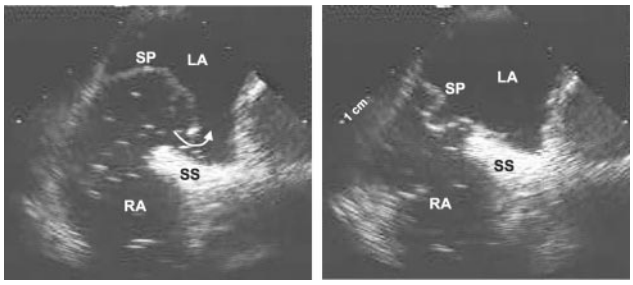


**Figure 5.** Atrial septal aneurysm demonstrated by TEE. The floppy part of the septum primum (SP) undulates freely between the left atrium (LA) and the right atrium (RA). The septum secundum (SS) is solid and immobile. On the left panel, bubbles cross through the PFO (arrow).

that the presence of a PFO alone increased the risk for recurrent events 5-fold, with an even higher risk in the presence of an atrial septal aneurysm.[16] Other studies have found no significant influence of an isolated PFO but show a strong influence by a PFO associated with an atrial septal aneurysm. In a trial randomizing patients to acetylsalicylic acid or coumadin, the individual presence of a PFO or an atrial septal aneurysm had no influence on the incidence of recurrent stroke.[20] These differing results on the question of whether a PFO with or without hypermobility of the septum leads to recurrent stroke are presumably related to factors (besides patient selection) such as diagnostic accuracy of the tests and definitions used to identify both the PFO and the atrial septal aneurysm.

Homma et al[25] identified other risk factors: (1) the presence of a Eustachian valve directed toward the PFO (Figure 3); (2) the gaping diameter of the PFO; and (3) the number of micro-bubbles present in the left atrium during the first seconds after release of a Valsalva maneuver during a bubble test.

## Catheter-Based PFO Closures

Initial techniques of percutaneous atrial septal defect closure were documented by King et al in the 1970s,[26] Rashkind in the 1980s,[27] and Sideris et al in the 1990s.[28] Bridges et al[29] 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. 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.[30,31] A randomized trial on the protective effect of transcatheter PFO closure in recurrent stroke patients has yet to be accomplished.

In 2000, the CardioSEAL device (NMT) and in 2002, the Amplatzer PFO Occluder (AGA) became available for PFO closure in high-risk patients in the United States. At least 5 additional devices have been used clinically abroad.[32]

The implantation can be performed with a single femoral venous puncture under fluoroscopy without echocardiographic guidance. The PFO can be passed 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 the left atrium. 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. The right-sided disk is then deployed and the device released. The perfect seat can be assessed before release by echocardiography or by hand-injected dye into the right atrium through the introducer (Figure 6). 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 TEE after a few months with a tight PFO and no evidence of thrombi on the device signals the cessation of all treatment and controls.

## Results With Transcatheter PFO Closure

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; however, none of these have occurred in the last 400 implantations done by the authors. Complete closure at follow-up can be expected in 90% to 95% cases with the 2 devices currently in use. Some trivial residual shunt may be acceptable, albeit undesirable, as

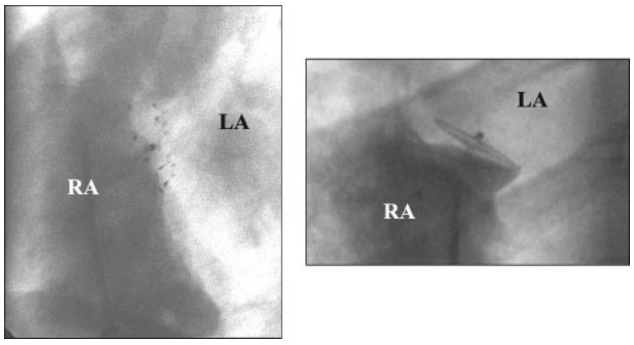


**Figure 6.** CardioSEAL device (left) and Amplatzer device (right) in perfect position ascertained with a manual dye injection into the right atrium (RA). There is no dye traversing into the left atrium (LA), proving that the septum primum is pulled tightly against the septum secundum.

the device will act as a filter for particulate matter.

Events have recurred in cases where 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.[31] In our experience, recurrent events may come close to the natural course for the first year (about 3%), after which they are extremely rare. In contrast, the natural course under platelet inhibitors or warfarin tends to have a steady or even increasing rate of events over the years.[21] Hence, the follow-up curves do seem to diverge in favor of device closure in nonrandomized comparisons.

## Conclusions and Outlook

Recurrent paradoxical embolism in the presence of a PFO associated with an atrial septal aneurysm is currently the only unequivocal indication for PFO closure. A percutaneous attempt should always precede surgical closure; the latter is unlikely to be rendered more difficult in case of a failed percutaneous attempt. None of the patients of the authors in the past 5 years required a surgical intervention. Hence, surgical PFO closure seems completely supplanted by the percutaneous approach. This is supported by the fact that recurrence rates for cerebrovascular accidents or transient ischemic attacks after surgical closure have been reported as 4%[32] to 20%[33] per year.

Because percutaneous closure may take less than 30 minutes under local anesthesia and can be performed as an outpatient procedure with very small risk and inconvenience for the patient, indications are bound to widen, especially if controlled trials and large series confirm that PFO closure reduces the life-long risk of recurrent stroke and perhaps other ailments.

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