STATE-OF-THE-ART PAPER

Patent Foramen Ovale

The Known and the To Be Known

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The patent foramen ovale (PFO) is a normal interatrial communication during fetal life that persists after birth in approximately 1 of every 4 adults. PFO is a potential route for embolic transit from the systemic venous circulation to the brain. Though there is compelling circumstantial evidence implicating PFO, the precise role of PFO in the pathogenesis of cryptogenic stroke is not yet established. Several randomized trials of transcatheter PFO closure versus medical management are ongoing. Results of these trials may improve our ability to select the best treatment for individual patients. Further well-designed studies are necessary to address several unresolved issues related to PFO stroke and PFO migraine pathophysiology, and to identify the patients who would most likely benefit from PFO closure. The purpose of this review is to summarize contemporary understanding, discuss current treatments, and explore some of the knowledge gaps pertaining to the clinical significance of PFO. (J Am Coll Cardiol 2012;59:1665–71) © 2012 by the American College of Cardiology Foundation

Prevalence and Anatomic Aspects

The patent foramen ovale (PFO) is an integral part of normal fetal circulation. Normally, a portion of the blood from the inferior vena cava passes from the right atrium to the left atrium through the PFO during fetal life, bypassing the lungs. Pulmonary blood flow increases greatly during neonatal circulatory transition, causing increased left atrial pressure. The resulting atrial pressure differences compress the septum primum against the septum secundum, functionally closing the PFO. Anatomic closure of the PFO occurs later in infancy in the majority of the population, but autopsy (1) and detailed contrast echocardiography studies demonstrate that anatomic closure is incomplete in approximately 1 of every 4 adults. Therefore, PFO should be considered a normal anatomic variant and not a pathological finding in the absence of possible paradoxical embolism or other specific clinical conditions.

PFO diameters in formalin-fixed hearts at autopsy range from 1 to 19 mm, and the average PFO size is larger in older adults (1). PFO anatomy is variable. The opening on the left atrial side tends to be crescentic in shape. In most cases, the flap-like septum primum barely covers the opening of the fossa ovalis when the septum primum is pushed toward the left atrial side of the septum. However, the length of the “tunnel” from the ridge of the fossa ovalis on the right atrial side to the left atrial opening can vary depending on the fixation location of the upper edges of the incompletely fused septum primum. The “flap” of the septum primum acts like a 1-way door, which can open a variable amount toward the left atrium depending on the force directing it in that direction, or seal the interatrial opening when it closes against the septum secundum. Under normal physiological conditions, the left atrial-to-right-atrial pressure differential gently pushes the thin septum primum against the septum secundum and, except for very brief periods in each cardiac cycle, seals the potential opening of the PFO. There is only trivial shunting of blood between the atria. Actions, such as the release of a Valsalva maneuver, can transiently reverse the normal left-to-right pressure gradient and cause an exaggerated transient leftward shift of the free edge of the septum primum with apparent enlargement of the orifice of the PFO. However, the actual maximal size of the opening of the PFO cannot be accurately measured without mechanically pushing the septum primum away from the septum secundum, either with a low-pressure balloon in the cardiac catheterization laboratory or with a probe during postmortem examination. The septum primum may be aneurysmal (Online Video 1) and may have single or multiple openings in addition to the gap of incomplete fusion with the septum secundum, which is the actual PFO.

The physiological implications of a PFO vary depending on loading conditions and streaming. Transthoracic or transesophageal echocardiography (TEE) or transcranial Doppler ultrasound has been used for diagnosis and assessment of
PFO (Figs. 1 and 2). Agitated saline contrast increases the diagnostic sensitivity by enhancing echocardiographic detection of the trivial intermittent right-to-left shunting across a typical PFO. Agitated saline contrast injected intravenously during Valsalva maneuver with release of straining when contrast is visualized in the right atrium increases sensitivity. Visualization of contrast microbubbles passing from the right to left atrium through the visualized foramen ovale during the release phase is diagnostic of an interatrial communication. In clinical practice, the actual site of right-to-left shunting may not be convincingly visualized or recorded for technical reasons. If a recording convincingly demonstrates microbubbles appearing in the left atrium immediately after arriving in the right atrium, then the presence of a PFO can be presumed (Online Video 2). If bubbles appear in the left atrium before or >5 beats after they appear in the right atrium, then the possibility of anomalous venous connection to the left atrium or pulmonary arteriovenous malformations must be considered.

Contrast injected through an upper extremity vein may be washed away by contrast-free blood flow from the inferior vena cava directed by the eustachian valve, creating a false-negative result (2). Injection of contrast via the femoral vein has been proposed to enhance detection by TEE, with the streaming effect of directed inferior vena cava flow to the region of the fossa ovalis and through a patent foramen (3).

**Figure 1** Schematic Image of PFO

The arrow indicates the location of the patent foramen ovale (PFO). See accompanying Online Video 1. LA = left atrium; LV = left ventricle; MV = mitral valve; RA = right atrium; RV = right ventricle; TV = tricuspid valve.

**Figure 2** Diagnosis of PFO

Intravenously injected agitated saline contrast increases the diagnostic sensitivity by enhancing transthoracic or transesophageal echocardiographic detection of the intermittent right-to-left shunting across the patent foramen. See accompanying Online Video 2. See text. bpm = beats/min; other abbreviations as in Figure 1.

**Relationship With Stroke**

Approximately 800,000 people experience stroke each year in the United States; approximately 610,000 of these are first attacks, and 185,000 are recurrent attacks (4). Transient ischemic attack (TIA), a temporary episode of neurological dysfunction likely caused by reduced blood flow to the brain or spinal cord without permanent damage to brain tissue, occurs in an additional 200,000 to 500,000 per year in the United States (4). However, definitions of TIA and stroke can vary somewhat depending on whether a clinical or anatomic viewpoint is used. Patients in many studies had not routinely had anatomic/brain magnetic resonance imaging (MRI) evaluations and were categorized as having had a TIA if they had transient clinical symptoms, even if an MRI was not performed or showed only small lesions.

There are multiple possible causes of ischemic strokes, and a clear etiology often cannot be found in the individual patient. It is estimated that approximately 25% to 40% of strokes are of undetermined pathogenesis, and are commonly termed cryptogenic strokes (CS). PFO is a potential route for embolic transit of platelet aggregations, thrombi, gas bubbles, or other particulate matter from the systemic venous circulation to the brain. PFO also could be a nidus for potentially embolic thrombus formation in situ.

The association of PFO with CS was first reported in 1988 by Lechat et al. (5). They studied the prevalence of PFO as detected by contrast echocardiography in 60 adults <55 years of age with ischemic stroke and compared the results with a control group of 100 subjects. The prevalence of PFO detected by their methodology was significantly higher in patients with stroke (40%) than in controls (10%).
Among those with no identifiable cause for their stroke, PFO prevalence was 56%; in those with no identifiable cause who had a risk factor (migraine, mitral valve prolapse, contraceptive usage), the prevalence was 40%; and in patients in whom a cause for stroke was identified, PFO prevalence was 21% (5). Petty et al. (6), in a TEE study of 116 patients with cerebral infarction, showed similar results. PFO was found in 40% of patients with infarcts of uncertain cause and in 25% of patients with infarcts of known cause. When the analysis was restricted to patients who underwent Valsalva maneuver, PFO with right-to-left or bidirectional shunt was found in 50% of patients with CS (6).

Several other studies have shown an association between PFO and CS (7–9), and have suggested a role for PFO in stroke pathophysiology. A meta-analysis of retrospective studies showed that patients <55 years who sustained a CS had a PFO prevalence 6 times greater than that of patients with other forms of stroke (10). Handke et al. (11) showed that the prevalence was higher among patients with CS than among those with stroke of known cause in both younger and older patients, suggesting paradoxical embolism as a cause of stroke. Taken together, these studies do suggest that PFO is more common in patients with a CS than in the general population (approximately 50% to 60% vs. 20% to 25%) or in patients with stroke of determined origin.

Despite the compelling circumstantial evidence implicating PFO in the pathogenesis of CS, prospective studies have not necessarily demonstrated an association. In a prospective population-based study by Meissner et al. (12), PFO was not found to be an independent risk factor for future cerebrovascular events in the general population after correction for age and comorbidity. This is not surprising, however, since PFO is found in about 25% of the general population, and only a tiny fraction of people with PFO may have the additional factors that increase the risk of an embolus traversing or forming in the PFO. Prophylactic closure of an incidentally discovered PFO is not recommended. A pooled analysis of prospective studies (8,13) did not find an increased risk of recurrent stroke among cryptogenic stroke patients with a PFO compared with those without PFO (14). However, this analysis does not address whether closure of a PFO in patients shown to be at risk for a paradoxical embolus (previous history) lowers the risk of recurrent stroke specifically in those patients. Small series of uncontrolled and relatively short-term evaluations have demonstrated a reduction in recurrence rate of focal neurological events in patients with an atrial septal defect or PFO who had experienced multiple recurrent events and underwent transcatheter defect closure (15).

Finally, optimal management of a thromboembolus caught in transit across a PFO (impending paradoxical embolism) is also not well defined. A systematic review of case reports and observational studies on this subject has compared mortality and systemic embolism between treatments (16). On multivariate regression models, surgical treatment demonstrated a nonsignificant trend toward improved survival compared with anticoagulation alone (16).

### Atrial Septal Aneurysm and PFO Size

The atrial septal aneurysm (ASA) is defined as a mobile protrusion of the septum primum tissue into the atrium measuring at least 10 to 15 mm or a phasic septal excursion of at least 15 mm occurring at some point during the cardiorespiratory cycle (17). Definitions for ASA vary widely in the literature (10–15 mm total excursion, 10 to 15 mm in 1 direction or the other, etc.). In our opinion, a 30-mm total excursion is too stringent a definition. A more accurate term may be atrial septal hypermobility since the septum really does not have a true aneurysm, but ASA is currently entrenched in the literature. ASA is frequently associated with PFO. In patients with cerebral ischemia and ASA, ASA (with or without PFO) is often the only potential cardioembolic source identified on TEE (18). Concomitant presence of an ASA, small additional atrial septal defects, a large eustachian valve, or Chiari strands have all been postulated (but not conclusively proven) to be significant in the presence of a PFO (19). Chiari strands, congenital remnants of the right valve of the sinus venosus, can be associated with both PFO and ASA, and are believed by some to facilitate paradoxical embolism (20).

The combination of PFO and ASA emerged as a predictor of increased risk for recurrent stroke in some reports (8,11), but in other studies, neither PFO alone nor in combination with ASA was associated with an increased risk for stroke (21). The association of ASA with stroke recurrence remains debatable. Homma et al. (13) demonstrated that neither the degree of shunt nor concomitant ASA is associated with an increased risk of stroke recurrence or death. Published literature is also inconsistent regarding foramen size as a CS risk factor. PFO maximal diameter during the Valsalva provocation has been shown on TEE in some studies to be greater in patients with CS (22), whereas others have not shown this association (13,23). Further studies are required to determine whether PFO size measured by any particular technique or other anatomic/physiological features are useful to stratify risk for CS.

### Recurrent Neurological Events and Therapy

The risk of stroke recurrence after CS justifies a search for effective preventive therapy. If PFO is felt to be a significant factor, then either the pathway for possible paradoxical embolization (the PFO) could be closed, or the formation of embolic material could be reduced (anticoagulate, stop scuba diving with techniques that allow nitrogen bubble formation, remove central lines, etc.). There are multiple options for either approach. In most series, the risk of recurrent CS with no form of treatment is approximately 6% to 8% annually (with or without PFO). With either medical treatment or PFO closure, the annual risk decreases to approximately 2% to 4%. That recurrences are not com-
pletely eliminated with either approach should not be surprising since CS undoubtedly has multiple, as yet unidentified, potential etiologies. PFO may be 1 etiology, but is seen in only about 50% of CS patients. About 20% of patients who have CS from unrelated causes are expected to have a PFO based on the incidence of PFO in the general population. The real question at this time is whether medical treatment, simple closure of the PFO or a combination of both approaches will be superior in terms of stroke prevention, costs, and patient tolerance in different subsets of patients.

**Surgical therapy.** The invasive nature of surgical intervention for prevention of CS in patients with PFO renders it generally less appealing than medical or transcatheter therapy. Risks of perioperative complications, including arrhythmias and bleeding, are significant technical hurdles. Minimal data regarding this approach has been collected. An annual combined stroke or TIA recurrence of 7.9% has been reported after surgical PFO closure (24). Though surgical closure of PFO is reportedly associated with a reduced risk of recurrent stroke, there are no large experiences. In addition, medical therapy is sometimes continued after surgery, which may affect stroke recurrence risk.

**Medical therapy.** The optimal medical therapy for prevention of recurrent CS is unknown. Numerous uncontrolled studies have shown an apparent benefit of medical therapy after a CS. However, the best medical treatment, antplatelet versus anticoagulant, remains controversial. WARSS (Warfarin–Aspirin Recurrent Stroke Study) was the first randomized controlled study to compare the effect of warfarin and aspirin after prior nondiabetic embolic ischemic stroke. WARSS showed aspirin was as good as warfarin in prevention of stroke recurrence, but presence of PFO was not specifically systematically evaluated (25). The majority of subgroup analyses in the WARSS showed no benefit of warfarin over aspirin. The PFO in Cryptogenic Stroke Study found no difference in time to recurrent ischemic stroke or death between patients randomized to aspirin or warfarin (13). Warfarin anticoagulation carries greater hemorrhagic risk and more complex monitoring and therapeutic adjustments, which can be a significant concern in many patients. Importantly, both medical treatments are reported to be associated with recurrent events after a CS. Annual stroke/TIA recurrence rates of 3.8% to 12% with medical treatment (oral anticoagulants or antiplatelet medication) have been reported in various studies (14,25–27).

**Transcatheter Therapy**

The possibility of avoiding or improving the outcomes of long-term anticoagulation is a potential benefit of PFO device closure. Since the first report in 1992 (15), several groups have described the safety and efficacy of PFO closure using various transcatheter devices. Defining PFO anatomy and careful evaluation of adjacent structures is important during transcatheter closure. Therefore, echocardiographic imaging (TEE or intracardiac echocardiography) plays a significant role for guidance during closure and is mandatory for achieving optimal results. Intracardiac echocardiography has the advantage of avoiding the need for general anesthesia.

Reported complications of PFO device closure include vascular injury, cardiac perforation or air embolization during implantation, device embolization, early and late thrombosis, and atrial arrhythmia. A large-sized device should not be used for closure as it may not conform well to the atrial anatomy, and may cause late complications by impinging on surrounding structures (28). With the use of contemporary devices, the incidences of complications are low, but not negligible (29). Most of these complications are preventable or transient and potentially can be avoided by continued improvements in technique and device design. At the present time, none of the available PFO closure devices have been approved by the U.S. Food and Drug Administration, and closures are performed off-label using devices approved for other indications.

An annual recurrence rate of 0% to 5% for stroke or TIA has been reported following PFO device closure (28,30,31). An organized literature review of nonrandomized studies found that the annual recurrence rate of stroke/TIA with PFO device closure was 0% to 4.9% versus 3.8% to 12.0% with medical therapy (27). Kutty et al. (28) analyzed the results of investigations performed for neurological events after PFO device closure and reported a combined recurrence rate of 3.4% for stroke/TIA and an event rate of 0.9% per year for recurrent strokes. These studies suggest that the recurrent stroke/TIA rates after PFO device closure are comparable to rates from studies of recurrent events in patients with PFO and CS treated with various regimens of medical treatment (8); however, PFO closure has not yet been proved superior to medical treatments. Despite enthusiasm for eliminating a theoretical cause of CS by PFO closure, patients deserve a clear presentation of the uncertain benefits of closing the PFO before proceeding. In discussions with patients, it has to be emphasized that the procedure would eliminate only 1 potential possible cause for stroke.

As of now, there is no clear evidence on the utility of transcatheter PFO closure devices in the treatment of patients with CS or TIA and PFO. Further studies are necessary to determine the potential efficacy of PFO closure devices in this setting and to identify the patients who are most likely to benefit from PFO closure.

**Randomized Trials**

Though the utility of transcatheter PFO devices for treatment of patients with CS and PFO is unknown, there are a wealth of uncontrolled data that show some improvement in recurrent stroke rates with PFO closure as compared with expected recurrence rates with no treatment. The magnitude of this benefit seems to be similar to improvements in
recurrence rates for medical treatments of patients who have suffered a first CS. This similarity in effect with suboptimal data is the ethical basis for currently ongoing randomized trials of PFO closure compared to medical management.

CLOSURE I (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), the first prospective, randomized, independently adjudicated PFO device closure trial, has just been completed (32). The trial was designed to test whether PFO closure using STARFlex device (NMT Medical, Boston, Massachusetts) plus medical therapy is superior to medical therapy alone for preventing recurrent stroke or TIA in patients with CS or TIA and a PFO. The trial consisted of 909 patients ≤60 years of age with a CS or TIA and a TEE-documented PFO, with or without ASA, randomized at 87 sites across the United States and Canada. All patients did not have MRI, and presence of stroke versus TIA was mostly made on clinical grounds. The primary endpoints were 2-year incidence of stroke or TIA, all-cause mortality for the first 30 days, and neurological mortality 31 days to 2 years.

CLOSURE I failed to demonstrate superiority of PFO device closure plus medical therapy (6 months of aspirin and clopidogrel followed by 18 months aspirin) over best medical therapy (24 months warfarin or aspirin or combination). The 2-year stroke rate was essentially identical in both study arms (3%), with no significant benefit shown in the device arm related to the degree of initial shunt or ASA. ASA was not shown to be a risk factor in this trial. Among patients in the device arm, there were major procedure-related vascular complications (3%), but it should be noted that many of the centers had little prior experience with transcatheter PFO closure techniques. There was a concerning rate of periprocedural atrial fibrillation (5.7%) with this particular device, which was not seen in other series from experienced centers using this and other devices. The trial concluded that an alternative explanation unrelated to paradoxical embolism is present in 80% of patients with recurrent stroke or TIA. This highlights the need for better standardized evaluations to detect alternative causes of CS and the need for further studies to examine the potential efficacy of PFO device closure in better-defined patient populations.

Three other trials, PC-Trial (Patent Foramen Ovale and Cryptogenic Embolism), RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment), and REDUCE (GORE HELEX Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients), are ongoing. The PC-Trial (NCT00166257) compares percutaneous closure of PFO using the Amplatzer PFO Occluder (AGA Medical Corp., Plymouth, Minnesota) versus antithrombotic treatment (warfarin for 6 months followed by antiplatelet agents). Randomization for the PC-Trial was stratified by patient age, presence of atrial septal aneurysm, and number of prior embolic events; the chosen primary endpoints being death, nonfatal stroke, and peripheral embolism. Patient enrollment for this trial was completed in 2009, and an interim analysis is expected in 2012. Endpoints of the RESPECT PFO trial (NCT00465270) are cerebrovascular accident or death. The REDUCE trial (NCT00738894) is designed to specifically compare antiplatelet therapy alone versus antiplatelet with PFO closure using the GORE HELEX septal occluder (W.L. Gore & Associates, Flagstaff, Arizona) and uses hard endpoints of brain MRI–confirmed recurrent stroke or TIA. Enrollment in the aforementioned randomized trials has been slow, possibly due to patient or physician preference for a variety of reasons. Off-label device closure of PFO outside of the trials is very common, particularly in subjects deemed to be high risk due to various reasons, including age or recurrence of neurological events. Even randomized trial results are only generalizable if the trial population is reasonably representative, so these practice patterns could spuriously influence future trial outcomes. There is clearly a need for more data to elucidate the best approach to the treatment of patients with CS and PFO.

**Relationship of PFO to Other Diseases**

PFO has been associated with the pathophysiology of several other disease states, including migraine headaches, decompression sickness, peripheral embolism including myocardial and renal infarction, and Alzheimer’s dementia. Right-to-left shunting through a PFO can also greatly worsen symptoms in patients with chronic lung diseases associated with hypoxemia, or obstructive sleep apnea/sleep-disordered breathing. In order of magnitude, the amount of right-to-left shunting to cause systemic desaturation is larger than the amount of shunting seen in the general population with a PFO.

**Migraines.** Del Sette et al. (33) first reported an association between migraine with aura and the presence of right-to-left shunts detected with transcranial Doppler. The presumed association of PFO with migraines relates to paradoxical embolism or humoral factors that escape degradation in bypassing the pulmonary circulation. Using transthoracic echocardiography, it was shown that among divers with decompression illness, those with large right-to-left shunts had a higher prevalence of migraine with aura in everyday life and after dives than those with no shunt or a smaller shunt (34). A retrospective evaluation of the effect of transcatheter closure of atrial shunts on migraine symptoms suggested a causal association between right-to-left shunts and migraine with aura, indicating that there may be a subgroup of patients who have severe migraine associated with a large right-to-left shunt in whom closure of the atrial defect may reduce or abolish symptoms (35). Others have reported complete resolution of migraines in 60% of patients and improvement in symptoms in 40% of patients after transcatheter closure of atrial shunts (36). Wahl et al. (37) evaluated migraine symptoms at a mean follow-up of 5
years in a retrospective cohort of patients who had transcatheter PFO closure for secondary prevention of paradoxical embolism. The prevalence of migraine with aura and the number of patients on migraine medication decreased significantly, suggesting beneficial reduction of symptoms, especially in migraine with aura (37).

No association was found between migraines and the presence of PFO in a recent, large case-control study (38). Moreover, a real benefit of PFO closure for reducing the frequency of migraines has not been shown in a randomized trial. The MIST (Migraine Intervention With STARFlex Technology) trial was a prospective, double-blind (control patients had a sham procedure and evaluating physicians were not supposed to be aware of whether a patient had a device) trial that evaluated the effectiveness of PFO closure in the treatment of migraine with aura (39). In MIST, 147 patients with a history of severe migraines and without any other indication for PFO device closure were randomized to undergo either device closure or a sham procedure. The patients were treated with aspirin and clopidogrel. No significant difference in the primary outcome of headache cessation was detected between the 2 groups 3 to 6 months after the procedure. On exploratory analysis, excluding 2 outliers, the closure group showed a greater reduction in migraine headache days compared with the sham group. These results could have been affected by several methodology and design reasons, including the selected primary efficacy endpoint, the duration of follow-up, and the medications used in both groups (39).

Two other trials, PRIMA (PFO Repair in Migraine With Aura) and PREMIUM (Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the Amplatzer PFO Occluder Compared to Medical Management), are currently under way. Further investigations are necessary to evaluate the causal relationship between migraines and PFO, and until definitive results are available the role of PFO device closure in the treatment of migraines is highly debatable.

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