The foramen ovale is an important fetal structure that is integral to fetal circulation. During fetal development days 30–37, intra-atrial endothelial cells proliferate to form the septum primum and the ostium primum. The overlap between these structures forms the inter-atrial passage allowing the fetal lungs to be bypassed by facilitating fetal blood movement from the right to the left atrium. The initiation of lung function and increase in left-sided pressures, both of which occur at birth, result in functional closure of the foramen ovale. In most people, spontaneous anatomical closure of the foramen ovale occurs in the first few months of life. However, based on several large autopsy studies, approximately 25 % of healthy adults in the general population have a patent foramen ovale (PFO),1,2 with equal prevalence between men and women. Most individuals with a PFO are asymptomatic. However, when the right atrial pressure increases so it is greater than the left atrial pressure, whether transiently (for example during a Valsalva maneuver) or permanently, a right-to-left shunt occurs across the PFO allowing the venous circulation to be in direct contact with the arterial circulation. This potential for a PFO to be open and have right-to-left flow means that paradoxical embolism to the coronary arteries is a significant risk. This article provides a focused up-to-date review of the association between cryptogenic stroke and PFO, diagnostic methods, recurrent stroke risk, clinical assessment scores, management approaches, and current guidelines.

**PFO Association with Stroke**

In the US, approximately 800,000 people suffer from a stroke annually, with around 185,000 being recurrent attacks. Stroke is the fifth leading cause of death, and the third leading cause of disability in the US.11 Eighty percent of all strokes are ischemic and 20–30 % are cryptogenic, meaning no obvious etiology is detected despite a detailed and thorough etiological work-up.12 PFO prevalence in cryptogenic stroke patients is greater (about 40 %) than in the general population, and even higher in cryptogenic stroke patients <55 years of age (about 55 %).13 The Risk of Paradoxical Embolism (RoPE) study devised a predictive model to determine the likelihood that an initial stroke was due to a PFO and recurrent stroke risk. However, observational studies suggest that stroke development in PFO patients is likely multifactorial.14–16 For example, atrial fibrillation and atrial flutter are established preventable ischemic stroke risk factors; therefore, the development of these arrhythmias in cryptogenic stroke patients with a PFO may increase the likelihood of stroke recurrence.17 In the 30 Day Event Monitoring Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event (EMBRACE) randomized controlled trial, cryptogenic stroke patients were monitored for atrial fibrillation and atrial flutter.
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fibrillation using a 30-day event-triggered loop recorder versus a 24-hour ECG Holter monitor. The authors found a significantly higher prevalence of atrial fibrillation in the cryptogenic stroke patients monitored for 30 days versus those monitored for only 24 hours after stroke (16.1 % versus 3.2 %; 95 % CI: 8.0–17.6; p<0.001). Thus, whether a PFO is present or not, it is important to carefully monitor for paradoxical atrial fibrillation in cryptogenic stroke patients and initiate appropriate anticoagulation for the prevention of recurrent stroke.

Multiple studies have established an association between PFO and cryptogenic stroke. The Risk of Paradoxical Embolism (RoPE) study devised a predictive model to determine the likelihood of initial stroke being due to the presence of PFO and to predict recurrent stroke risk. The premise of the RoPE study was that patients with a high RoPE score and significant stroke recurrence risk would benefit the most from PFO closure for secondary stroke prevention. Using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification of cryptogenic stroke, Kent and Thaler used data from 3,023 cryptogenic stroke patients from 12 independent databases to derive a RoPE score calculator utilizing six patient characteristics (hypertension, diabetes mellitus, prior stroke/transient ischemic attack (TIA), non-smoker, cortical infarct on brain imaging, and age) to predict the probability that the stroke is PFO-related as opposed to the PFO being an incidental finding. While RoPE score is not advocated as a definitive tool to determine PFO management, it is a validated model that predicts the extent of PFO contribution to stroke causation. Stroke patients with RoPE scores of seven or greater have a paucity of traditional stroke risk factors, and therefore are more likely to benefit from PFO closure as a means to reduce the risk of recurrent stroke.

Diagnosis

A PFO is rarely detected on a routine transthoracic echocardiogram (TTE) unless one is specifically looking for it. Findings suggestive of PFO on a TTE include hypermobility of the inter-atrial septum (atrial septal aneurysm), and color flow Doppler findings of left-right or bi-directional flow across the atrial septum. Confirmation of a PFO is routinely accomplished by TTE with bubble contrast injection. In this study, agitated saline injected intravenously at rest and during the release of the strain phase of the Valsalva maneuver is performed during 2D echocardiographic imaging focused on the inter-atrial septum. With visualization of the entire heart with 2D echocardiography, the injected saline increases blood pool echodensity and creates visible microbubbles, first seen in the right atrium. In a normal individual, no microbubbles will be seen in the left atrium. If a PFO is present, the saline microbubbles will subsequently be seen in the left atrium within the first three cardiac cycles at rest, with release of a Valsalva maneuver, or in both instances. The prompt appearance of contrast in the left atrium following venous injection is considered a positive bubble study for intra-cardiac shunting. The size of the PFO is often determined by the number of microbubbles visualized in the left atrium during the first three initial cardiac cycles. Saline microbubbles seen after five to six cardiac cycles after injection or release of Valsalva strain usually indicate the presence of pulmonary arteriovenous malformations. The sensitivity for PFO detection with a TTE bubble study is 50 %. The gold standard for the identification and diagnosis of a PFO is a transesophageal echocardiogram (TEE). This is because it enables direct visualization of the PFO anatomy and the microbubbles entering the PFO tunnel and traversing into the left atrium during the bubble study. Color flow Doppler during TEE is also used to directly visualize the shunting of blood. Schneider et al. determined a sensitivity and specificity of 100 % for color Doppler TEE as well as 89 % sensitivity and 100 % specificity for contrast-enhanced TEE. The American Academy of Neurology recommends the use of a contrast-enhanced TEE for the detection of a PFO and inter-atrial shunting for the potential cause of stroke. Other imaging modalities that may be considered for the detection of a PFO include transcranial Doppler with bubble contrast injection (which is less frequently used), multi-detector computed tomography, or cardiac MRI.

Several anatomical features accompanying PFO have been associated with recurrent stroke. Inter-atrial septal aneurysm (ASA) is a hypermobile atrial septum that results in significant movement of at least 10 mm from the plane of the septum into either the right or left atrium. While ASA occurs in 2.2 % of the general population, it occurs in approximately 60 % of cryptogenic stroke patients with PFO. However, it is not clear what the exact mechanism is by which an ASA affects cryptogenic stroke risk in the setting of a PFO. The anatomical size and physiological shunt size of the PFO are also potential predictors of stroke recurrence. A PFO of >4 mm on TEE has been associated with a greater odds ratio for stroke. TEE defines PFO size as the maximal height of separation between the septum primum and secundum. The physiological shunt size of a PFO is determined by the number of bubbles that cross the PFO, with large PFO shunts being defined as >20 microbubbles. However, evidence of a correlation between PFO anatomical size, physiological shunt size and stroke risk varies.

Management of PFO After Stroke

Based on the results of three completed clinical trials, the recurrence rate of ischemic stroke in patients with PFO and medically-treated cryptogenic stroke ranges between 0.6 % and 1.5 % per year. There are limited data comparing antiplatelet therapy with anticoagulation in cryptogenic stroke patients with PFO. The PFO in Cryptogenic Stroke Study (PICSS) was a sub-study of the Warfarin-Aspirin Recurrent Stroke Study (WARSS), a multi-center study in which stroke patients were randomized to either warfarin or aspirin and monitored for stroke recurrence or death over a 24-month period. Of the 2,206 stroke patients, 630 underwent TEE evaluation for clinical purposes including cryptogenic stroke. These 630 patients were then enrolled in the 42-center PICSS study and randomly assigned to treatment with warfarin or aspirin. Their TEE images were evaluated for the presence of PFO. The two primary endpoints of the study were recurrent ischemic stroke or death from any cause. In the study, 312 patients were randomized to warfarin and 318 to aspirin. Of the participants, approximately one-third (203 patients) were diagnosed with a PFO. Only 98 of the 203 patients were diagnosed with cryptogenic stroke. In this small group of PFO patients, a high recurrent event rate was observed on medical therapy, with no significant difference in time to primary endpoints between the warfarin- and the aspirin-treated patients (hazard ratio [HR] 1.29; 95 % CI: 0.63–2.64; 2-year event rates 16.5 % versus 13.2 %; p=0.49). More patients taking warfarin reached the primary endpoint, however the difference was not significant. The updated 2014 American Heart Association/American Stroke Association (AHA/ASA) guidelines have a Class I, Level of Evidence (LOE) B indication
for antiplatelet therapy in ischemic stroke/TIA patients with a PFO as well as a Class I, LOE A for anticoagulation in patients with an ischemic stroke/TIA with a PFO and an established PFO.41,42

Despite medical therapy, the stroke recurrence rate in ischemia stroke patients with PFO is estimated at 4.5% within a 4-year period.40 In PICSS, the incidence of recurrent stroke in PFO patients with ischemic stroke was substantially higher, being 14.8% at 2 years.43 Therefore, in addition to medical therapy, the utility of secondary preventative treatment options such as percutaneous PFO closure has been a topic of debate. Observational data, including meta-analysis of observational studies on PFO closure therapy, point to the safety and low stroke recurrence rate compared to medical treatment alone.44-47 As controversy exists over the preferred management strategy for secondary prevention in patients with PFO and prior stroke, randomized clinical trials (RCTs) have been performed to evaluate the safety and efficacy of percutaneous PFO closure in this patient population. There are three well-known completed multi-center RCTs comparing PFO closure using one of two devices – the umbrella occlude (STARFlex™, NMT Medical, Inc.) or the disc occlude (AMPLATZER™ PFO Occluder, AGA Medical/St. Jude Medical) – to medical therapy alone for the prevention of recurrent ischemic stroke in patients with a history of cryptogenic ischemic stroke.48,49,50 The Closure I trial6 evaluated the STARFlex PFO closure system against the administration of warfarin, aspirin, or combined aspirin and warfarin. The Randomized Evaluation of Recurrent Stroke Comparing PFO Closure To Established Current Standard of Care Treatment (RESPECT) trial37 compared the AMPLATZER PFO Occluder with four treatment regimens: monotherapy with warfarin, aspirin or clopidogrel, or a combination of aspirin with extended-release dipyridamole. The percutaneous closure trial38 compared the AMPLATZER PFO Occluder with any antiplatelet or anticoagulation therapy of the physician’s choice. At the time of completion and initial data evaluation, none of these trials had found a statistically significant benefit of PFO closure over medical therapy for ischemic stroke recurrence. Additionally, there was a significantly higher incidence of atrial fibrillation development in the patients who received the STARFlex closure device, but not the AMPLATZER PFO Occluder, compared to medication. Based on these three RCTs, the 2014 AHA/ASA guidelines did not recommend PFO closure in cryptogenic stroke (Class III, LOE A).51 The American Academy of Neurology maintained a strong position against routine PFO closure in cryptogenic stroke patients outside of research trials until July 2016, when an updated statement was issued discouraging its use.48 However, it is important to note that the statement was made prior to the publication of positive data on PFO closure from the three trials in September 2017,52,53 and further update of their position on the topic is likely.

The final long-term results of the RESPECT trial were presented at the 2016 Transcatheter Technologies Annual Scientific Meeting in Washington, DC, and have since been published.46 The investigators noted a relatively low incidence of recurrent stroke in both treatment groups during the initial follow-up period.46 In the intention-to-treat cohort, a total of 25 primary endpoint events occurred (nine in the closure group and 16 in the medical therapy group), all of which were recurrent fatal or non-fatal stroke (0.66 events per 100 patient-years, HR with closure = 0.49, 95% CI: 0.22–1.11; p=0.08).37 The investigators followed the study population for longer to assess for divergent results. The investigators reported that after 10 years, in an intention-to-treat analysis, PFO closure with the AMPLATZER PFO Occluder resulted in a 62% relative risk reduction (RRR) for recurrent ischemic stroke compared to medical management (HR 0.38; 95% CI: 0.18–0.79; 10-year event rates 2.3% versus 11.1%; p<0.001).47 Similar results were seen in patients <60 years of age (58% RRR; HR 0.42; 95% CI: 0.21–0.83; 10-year event rates 3.0% versus 13.2%; p=0.01).48 The rates of atrial fibrillation, major bleeding, and death from any cause were comparable or lower in the device study arm. In October 2016, the US Food and Drug Administration approved the AMPLATZER PFO Occluder for percutaneous transcatheter PFO closure to reduce the risk of recurrent ischemic stroke in patients, predominantly between 18 and 60 years, who have had a cryptogenic stroke due to presumed paradoxical embolism, as determined by a neurologist and cardiologist following evaluation excluding all other known causes of ischemic stroke.

In May 2017, at the third European Stroke Organisation Scientific Meeting in Prague, Czech Republic, the primary results of two multicenter randomized controlled trials – Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE) and GORE® HELEX® Septal Occluder/GORE® CARDIOFORM Septal Occluder for PFO Closure in Stroke Patients (REDUCE) – evaluating PFO closure with antiplatelet therapy versus antiplatelet therapy alone were presented.51,52 Both trials provided new support for PFO closure in cryptogenic stroke by achieving their primary endpoints.51,52 Kasner presented the REDUCE trial, stating that through at least 2 years, PFO closure with the GORE HELEX or GORE CARDIOFORM (both W.L. Gore & Associates) septal occluder plus antiplatelet therapy was superior to antiplatelet treatment alone in reducing the risk of recurrent (77% RRR; HR 0.23; 95% CI: 0.09–0.62) and new clinical ischemic stroke or in silent brain infarct on MRI (49% RRR; HR 0.51; 95% CI: 0.29–0.91).43 As seen in some prior studies, the REDUCE trial showed that significantly more patients in the PFO closure group developed new-onset atrial fibrillation/flutter compared to the antiplatelet-only group (6.6% versus 0.4%; p<0.001).46 The CLOSE study, a multicenter randomized superiority trial, compared transcatheter PFO closure with any CE-mark PFO closure device plus antiplatelet therapy to antiplatelet therapy alone for the prevention of recurrent stroke in patients aged 16–60 years who had a recent cryptogenic ischemic stroke attributed to PFO with an associated atrial septal aneurysm or large right-to-left shunt.44 This trial also had positive results in which recurrent fatal or non-fatal stroke was significantly reduced in the PFO closure group as compared with the antiplatelet therapy alone group (97% RRR; HR 0.03; 95% CI: 0.00–0.26; p<0.001).53 The CLOSE trial showed a significantly higher rate of new-onset paroxysmal atrial fibrillation in the PFO closure group compared to the antiplatelet only group (4.6% versus 0.9%; p<0.02).44 It is important to note that in both studies, the new-onset atrial fibrillation was peri-procedural (detection within 45 days of the procedure), with no atrial fibrillation recurrence noted in the CLOSE PFO patients at median follow-up of 4.4 years, and no detection of atrial fibrillation at 2 weeks from onset in 59% of the PFO patients who developed the arrhythmia in the REDUCE study. However, it is important to note that these findings cannot yet determine the stroke risk attributable to atrial fibrillation induced by PFO closure.

Although the Closure I trial, percutaneous closure trial, and early follow-up results of the RESPECT trial were not able to show the superiority of PFO closure over medical therapy alone in the prevention of stroke
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recurrence in patients with PFO, the benefit of PFO closure compared to medical therapy alone for the secondary prevention of cryptogenic stroke laid the groundwork for the positive results from the CLOSE, REDUCE and RESPECT trials. These three trials have shown exciting, encouraging and compelling evidence that PFO closure reduces the risk of recurrent stroke and provide strong supportive data for the ongoing debate on PFO closure in cryptogenic stroke.

PFO and Unique Clinical Scenarios

Migraines are common phenomena, with a prevalence of approximately 18% and 6% in women and men, respectively. Several studies have documented a high co-existence of migraine headaches and PFO: PFO is present in up to 60% of migraine patients; and up to 50% of patients documented a high co-existence of migraine headaches and PFO: PFO is present in up to 60% of migraine patients; and up to 50% of patients with PFO suffer from migraines. A number of early trials evaluating PFO closure for secondary stroke prevention showed a trend of decreased migraine incidence after PFO closure. These observational studies suggested that patients with migraine were the most likely to experience complete resolution of migraine with PFO closure. Furthermore, a recent meta-analysis found that after PFO closure, migraine improvement was greater in patients who had migraine with aura than in those without aura. Thus Shi et al. suggest the presence of aura serves as a predictor for symptom improvement after PFO closure. However, this is a retrospective analysis and prospective randomized controlled trials are necessary to show whether aura has a prognostic value for patient outcomes. Previously, three RCTs – Migraine Intervention with STARFlex Technology (MIST), Percutaneous Closure of PFO in Migraine with Aura (PRIMA), and Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management (PREMIUM) – were performed to assess the potential benefit of PFO closure on reducing or eliminating migraines. All three studies had negative results, with no significant difference in the reduction or cessation of migraines between the treatment and control groups. Based on current evidence, PFO closure is not recommended as a preventive treatment for migraine.

There is a known association between PFO and increased risk of decompression illness in scuba divers. Professional divers or military personnel may undergo screening for PFO with a bubble contrast TTE or TEE study. The presence of a PFO is considered necessary to show whether aura has a prognostic value for patient outcomes. Previously, three RCTs – Migraine Intervention with STARFlex Technology (MIST), Percutaneous Closure of PFO in Migraine with Aura (PRIMA), and Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management (PREMIUM) – were performed to assess the potential benefit of PFO closure on reducing or eliminating migraines. All three studies had negative results, with no significant difference in the reduction or cessation of migraines between the treatment and control groups. Based on current evidence, PFO closure is not recommended as a preventive treatment for migraine.

Platypnea-orthodeoxia is an unusual clinical scenario that is the inverse of orthopnea, whereby affected individuals develop hypoxemia when assuming an upright position. The condition is created by circumstances wherein right–left shunting through a PFO or atrial septal defect is enhanced when the person is upright. The various scenarios associated with this condition typically result in transient increases in right atrial pressure and decreases in right ventricular compliance, favoring right-to-left shunting through a PFO or the atrial septal defect. The presence of intracardiac shunting, intrapulmonary shunting, ventilation-perfusion mismatch, or a combination of these conditions – as seen with kyphoscoliosis, tortuous aortic root and ascending aorta, aortic elongation, or hemidiaphragmatic paralysis – can lead to right–left shunting and hypoxemia. Platypnea-orthodeoxia is a rare condition with <100 cases reported worldwide. Isolated citations in the scientific literature detail case reports where atrial septal defect or PFO closure resulted in resolution of positional hypoxemia. The 2008 ACC/AHA guidelines for the management of adults with congenital heart disease have a Class IIa, LOE B indication for reasonable closure of an atrial septal defect, either percutaneously or surgically, in the presence of documented platypnea-orthodeoxia.

Conclusion

PFO is in and of itself a paradox, in that it is a very common remnant of the fetal circulation, present in up to 25% of adults, and is usually associated with a benign clinical scenario and lack of adverse effects. However, the presence of a PFO defect in association with venous thromboembolism can lead to paradoxical embolism from the venous to arterial circulation, with serious consequences. While the majority of individuals with a PFO never experience adverse sequelae, it is the most likely contributing factor to cryptogenic stroke in those <55 years old and when common risk factors for stroke are absent. The RoPE score is an accurate, validated tool to help determine the likelihood that cryptogenic stroke is due to a PFO. The final decision about PFO management is not necessarily predicated by RoPE score results, and each case should be individually considered with input from cardiology and neurology about how best to treat a specific patient. Current AHA/ASA guidelines recommend antiplatelet therapy in all cryptogenic stroke patients with PFO. In the past, early results from randomized PFO closure versus medical therapy trials showed no significant decrease in the rate of recurrent stroke with PFO closure in cryptogenic stroke patients. However, longer-term follow-up data and newer trials have shown a significant decrease in the incidence of recurrent ischemic stroke with PFO closure as compared to medical therapy alone. This has led to the US Food and Drug Administration approval of the AMPLATZER PFO Occluder in PFO-related cryptogenic stroke patients, and anticipation that the GORE HELEX device will be approved in the near future. Continued trials and long-term follow-up are needed to further solidify and clarify the benefit of PFO device closure in the cryptogenic stroke population. Patients will benefit the most from collaboration between cardiologists and neurologists in the management of this unique clinical situation.
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