Persistent pathology of the patent foramen ovale: a review of the literature

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In the fetal circulation, the foramen ovale is a necessary communication allowing shunting of blood from the right to the left atrium.1 At birth, blood returning from the pulmonary circulation increases, causing closure of the foramen ovale.1 However, in 20–34% of the general population, a patent foramen ovale (PFO) persists.1

In most cases, PFOs are not pathogenic, but if the shunt across a PFO is significant, complications can occur.2 We searched the literature for studies exploring the indications, approaches and complications of PFO closure (Supporting Information, appendix I). For optimal treatment, clinicians should consider the risks and benefits surrounding PFO closure.

Indications for closure

There are multiple indications for PFO closure. The most widely studied are PFO-associated ischaemic stroke and migraine. Other indications include platypnoea–orthodeoxia syndrome, decompression illness, paradoxical embolism, closure before neurosurgery, carcinoid syndrome and unexplained postoperative hypoxia (Supporting Information, table I).

PFO-associated stroke

Stroke is the leading cause of preventable disability worldwide and the fifth most common cause of death in Western societies.3 The term PFO-associated stroke has been proposed to describe the distinct entity of superficial, large deep, or retinal infarcts causing ischaemic stroke in the presence of a medium to high risk PFO and no other likely cause.4

The Risk of Paradoxical Embolism (RoPE) score is an assessment tool that evaluates the risk of a PFO-related stroke.5 Scores are based on absence of hypertension, absence of diabetes mellitus, no history of stroke or transient ischaemic attack (TIA), non-smoking status, presence of cortical infarct on imaging, and age categories.6 It is crucial to exclude atrial fibrillation before PFO-closure given its high prevalence (~15%). Studies have shown that 24-hour monitoring should be taken at least 30 days before consideration of PFO closure.5,7 It has been suggested that patients with right-sided endocardial pacemaker leads should be assessed for PFOs due to increased risk of stroke,8 but other studies have found no significant difference.7,9 Two important factors not covered by the RoPE score are PFO shunt size and presence of an atrial septal aneurysm, with a greater effect of PFO closure preventing stroke recurrence for patients with these anatomical features (relative risk [RR], 0.27; 95% CI, 0.11–0.70; I² = 42%) compared with patients without these features (RR, 0.80; 95% CI, 0.43–1.47; I² = 12%).10 In particular, a 2020 meta-analysis suggested that an atrial septal aneurysm (Box 1) — interatrial septum area greater than 10 mm in width that moves away from the normal plane of the septum by at least 10 mm — was a more important predictor for recurrent stroke than shunt size and was independently associated with recurrent PFO-related stroke (hazard ratio [HR], 3.27; 95% CI, 1.82–5.86).11

Two main mechanisms of PFO-associated stroke are described in the literature: “atrial fibrillation-like” pathophysiology and paradoxical embolism.14,15 which are both exacerbated by an atrial septal aneurysm. In patients with PFOs and large atrial septal aneurysms, the left atrium was demonstrated to have an “atrial fibrillation-like” pathophysiology, which was postulated to cause an increased risk of stroke.15 The same authors found left atrial dysfunction reversed after PFO closure.11 An alternative hypothesis describes PFOs causing transient right-to-left shunt leading to paradoxical embolism of venous emboli, causing ischaemic strokes.12 An atrial septal aneurysm can facilitate paradoxical embolism by widening the PFO and redirecting blood flow from the inferior vena cava towards the PFO.12 Box 2 shows a large thrombus from the right atrium extending into the left atrium.

PFO closure for cryptogenic stroke has been studied extensively in the past two decades. Early randomised controlled trials such as CLOSURE I (Evaluation of the STARFlex Closure System in Patients with a Stroke and/or TIA due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale) and the PC Trial (Clinical Trial Comparing Percutaneous Closure of Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism) failed to demonstrate a significant reduction in recurrent stroke risk in patients undergoing PFO closure.13,14 The PC Trial was conducted in 29 sites and compared the Amplatzer occluder (Abbott) with medical therapy. The primary endpoint occurred in seven patients of the closure group compared with 11 in the medical therapy group, but this difference was not statistically significant (HR, 0.63; 95% CI, 0.24–1.62).15

Summary

- A patent foramen ovale (PFO) is an interatrial shunt, with a prevalence of 20–34% in the general population.
- While most people do not have secondary manifestations of a PFO, some reported sequelae include ischaemic stroke, migraine, platypnoea–orthodeoxia syndrome and decompression illness. Furthermore, in some cases, PFO closure should be considered for patients before neurosurgery and for patients with concomitant carcinoid syndrome.
- Recent trials support PFO closure for ischaemic stroke patients with high risk PFOs and absence of other identified stroke mechanisms.
- While PFOs can be associated with migraine with auras, with some patients reporting symptomatic improvement after closure, the evidence from randomised controlled trials is less clear in supporting the use of PFO closure for migraine treatment.
- PFO closure for other indications such as platypnoea–orthodeoxia syndrome, decompression illness and paradoxical embolism are based largely on case series with good clinical outcomes.
- PFO closure can be performed as a day surgical intervention with high procedural success and low risk of complications.

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There were several limitations identified in both the PC and CLOSURE I trials. For the PC Trial, limitations included the inclusion of TIA and peripheral embolism as endpoints, lack of blinding during recruitment, inclusion of patients receiving anticoagulation, and inclusion of grade 1 shunts. With the CLOSURE I trial, more than one-quarter of participants had TIAs, and patients at highest risk for paradoxical embolism were excluded, as they would be confounded by long-term anticoagulation therapy. Furthermore, CLOSURE I assessed the STARFlex (NMT Medical) system for PFO closure. However, this device is no longer manufactured and had high rates of residual shunt and higher rates of periprocedural complications, which may have contributed to the non-significant endpoint.

The RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial was the first randomized controlled trial that showed PFO closure to be superior to medical therapy (HR, 0.55; 95% CI, 0.31–0.99), and a number-needed-to-treat of 42 to prevent one ischaemic stroke. Further meta-analyses of this patient population group (n = 10 327) have shown that medical therapy was associated with a 6.3-fold increase in recurrent neurological events.

The CLOSE (PFO Closure or Anticoagulants v Antiplatelet Therapy to Prevent Stroke Recurrence) trial reported a lower rate of recurrent stroke in the PFO closure group compared with medical therapy (0% v 6.0%; HR, 0.03; 95% CI, 0–0.26). Importantly, this trial included all commercially available devices for PFO closure in Europe. Finally, the DEFENSE-PFO (Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients with High-Risk Patent Foramen Ovale) trial assessed the Amplatzer PFO occluder versus optimal medical therapy in patients with a high risk PFO (atrial septal aneurysm, hypermobility of the interatrial septum or > 2 mm in size). The primary endpoints only occurred in the medical therapy arm (2-year event; 12.9%; \( P = 0.013 \)). This trial highlights the importance of PFO closure in this select at-risk population group.

Persistent PFOs can occur after device insertion. A 2014 study (n = 934) with PFO closure devices found 100% procedural success rates, with 86% of patients having no residual shunt at 6-month follow-up. Residual shunt at 6 months was higher in the patients with the Cardia device (31% of patients) compared with the Amplatzer device (9% of patients; \( P < 0.001 \)), but without significant differences in the clinical endpoints of stroke, TIA and peripheral embolism, and no significant differences in procedural complications rates. A residual shunt is also more common in the presence of an atrial septal aneurysm (odds ratio [OR], 7.6; 95% CI, 1.38–42.35). Post-closure monitoring with a transthoracic echocardiogram is crucial, specifically the day after device implantation and with a follow-up contrast transthoracic echocardiogram or transoesophageal echocardiogram at 6 months to exclude residual shunt.

Migraine

It has been proposed that migraines are associated with PFOs with right-to-left cardiac shunts. The presence of auras may identify a subset of patients with migraine who are more likely to benefit from intervention. Although unclear mechanistically, theories include paradoxical embolism causing cerebral ischaemia and delivery of vasoactive substrates. Three major randomized controlled trials have investigated the effectiveness of PFO closure for migraines: the MIST (Migraine Intervention with STARFlex Technology) trial, the PRIMA (Percutaneous Closure of PFO in Migraine With Aura) trial, and the PREMIUM (Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management) trial.
The MIST trial found no significant impact of PFO closure on its primary outcome of migraine cessation (n = 147) with moderate or large PFOs. However, its investigators were criticised for methodological shortcomings and trial misconduct. The PRIMA trial (n = 107) used optimal medical therapy as the control group and did not find a significant difference in the reduction in number of migraine-days per-month. The PREMIUM trial also did not find a significant difference for its primary outcome of 50% reduction in the monthly number of migraine attacks. The current evidence to support PFO closure for symptomatic relief of migraines is unclear.

Other indications

**Platypnoea–orthodeoxia syndrome**

Platypnoea–orthodeoxia syndrome is characterised by dyspnoea and hypoxaemia in an upright position that resolves when supine. Causes of platypnoea–orthodeoxia syndrome include PFOs, atrial septal defects, lung parenchymal diseases and intrapulmonary arteriovenous dysfunction or hepatopulmonary syndrome. In PFO-associated platypnoea–orthodeoxia syndrome the theorised mechanism is interatrial septal distortion on upright position which changes its relationship to the inferior vena cava and eustachian valve, leading to increased blood flow from the inferior vena cava through the septal defect. Confirmation requires a transoesophageal echocardiogram with bubble study, in both supine and sitting/upright position, and should demonstrate right-to-left shunting at rest. A case series (n = 54) concluded that percutaneous PFO closure led to improvement in oxygen saturations (mean oxygen saturation on room air pre-procedure, 81% ± 8%; mean post-procedure, 95.1% ± 0.5%).

**Decompression illness**

Symptoms of decompression illness occur when gas bubbles enter the arterial circulation by effectively bypassing the pulmonary filtration mechanism through a PFO and right-to-left shunt. An observational study demonstrated that PFO closure led to the elimination of arterial bubbles after simulated dives. This also manifests clinically, as a prospective non-randomised controlled trial of 104 divers with a history of decompression illness (including 26 divers with PFO who had PFO closure and 39 with PFO who did not have PFO closure) found that PFO closure prevented neurological symptoms of decompression illness.

**Paradoxical embolism**

Paradoxic embolism occurs when a dislodged venous thrombus enters the systemic circulation via an intracardiac or pulmonary shunt, potentially resulting in multi-organ ischaemia and infarction. In patients with pulmonary embolism, PFOs (> 4 mm) increase the risk of systemic embolism by fivefold and the risk of death by tenfold compared with patients without PFOs. Paradoxic embolisms can occur in the non-cerebral circulation, including the coronary arteries, visceral organs and limbs. Iatrogenic material, such as in sclerotherapy, can also cause paradoxical embolism. PFO closure in these circumstances should be assessed case by case, especially when some patients may require lifelong anticoagulation if PFO closure is deemed not beneficial.

**Before neurosurgery**

A PFO is traditionally considered a contraindication for neurosurgery performed in the semi-sitting position, which is primarily used for procedures of the posterior fossa or cervical spine. As there is an increased chance of venous air embolism perioperatively due to the patient’s position, a PFO may lead to paradoxical embolism to the heart or brain through the right-to-left shunt. A systematic review of studies (four studies, n = 977) found that air embolism occurred in 40.2% of patients with PFO during posterior fossa or cervical spine neurosurgery in the semi-sitting position. The authors suggest preventive PFO closure may be indicated in patients with a large PFO, permanent shunt, or history of paradoxical embolism.

**Postoperative unexplained hypoxaemia**

There have been multiple case reports of hypoxaemia due to acquired right-to-left shunts in patients with a PFO following thoracic or laparoscopic abdominal surgery. While not completely understood, patients who develop unexplained hypoxaemia after the operation should be considered for a transthoracic echocardiogram and bubble study to assess for PFOs.

**Associated carcinoid syndrome**

Carcinoid tumours can induce valvular heart disease known as carcinoid heart disease through a fibrotic process. While right-sided carcinoid heart disease is more common due to the pulmonary inactivation of serotonin, a PFO and right-to-left shunt may lead to left-sided carcinoid heart disease. A case series (n = 3) suggested percutaneous PFO closure should be considered in patients experiencing systemic deoxygenation in the setting of carcinoid heart disease. After PFO closure, patients had improved New York Heart Association functional class (mean class pre-procedure, 3.67 ± 0.58; post-procedure, 2.33 ± 0.58) and 6-minute walk test results (mean walking distance pre-procedure, 377 ± 45 m; post-procedure, 460 ± 72 m; P = 0.03), despite participants having residual right-to-left shunts.

**Approach to therapy**

The initial investigation when suspecting a PFO is a transthoracic echocardiogram with a positive bubble study during rest or Valsalva manoeuvre. A transoesophageal echocardiogram is the gold standard for PFO assessment to confirm the defect, assess size, confirm presence of an atrial septal aneurysm and determine the most appropriate closure method. Alternatively, PFO diagnosis can be made through invasive guidewire evidence where the interatrial septum is crossed at the level of the PFO. In some circumstances, such as a complicated (associated with other cardiac abnormalities) or very large (> 3 cm) defect associated with extreme atrial septal aneurysm, surgical referral is occasionally indicated.

Percutaneous PFO closure commonly occurs as a day procedure in an experienced centre under conscious sedation with fluoroscopic guidance. In some cases, a general anaesthetic may be necessary especially if a transoesophageal echocardiogram is used where septal anatomy is challenging. A multipurpose catheter is inserted via the femoral vein with or without a 0.035 inch guide wire support and advanced until the PFO is crossed. Once the appropriate closure device is selected, it is inserted within the delivery sheath through the access site, and the left atrial disc is expanded followed by retraction of the delivery system and then deployment of the right atrial disc (Box 3). In some cases intraprocedural echocardiogram is required to confirm the positioning of the closure device. If the position is satisfactory, the closure
Patients with PFO-associated stroke should receive aspirin lifelong. Generally, continue dual antiplatelet therapy for 3–6 months, and patients should be followed up by a cardiologist. Complications of percutaneous PFO closure include device-related complications such as device migration, occlusion, or malposition.

Conclusions

PFOs are common in the general population and, although rare, can lead to several pathologies. Recent studies have shown PFO closure to be an effective treatment for PFO-associated stroke. While the evidence for routine closure for other indications such as migraine is less robust, smaller studies suggest patients can benefit from PFO closure in select situations. PFO closure is generally well tolerated with very high rates of closure success and low complication rates. Further research is required to identify subgroups who may further benefit from PFO closure.

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Supporting Information

Additional Supporting Information is included with the online version of this article.