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REVIEW ARTICLE

The Multiple Clinical Manifestations of Patent Foramen Ovale

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ABSTRACT

A patent foramen ovale (PFO) is a congenital remnant of the fetal circulation that persists in 25% of adults. Once considered a mostly benign congenital heart defect, the presence of PFO-mediated right-to-left shunt has been associated with several clinical conditions, including cryptogenic stroke, migraine with aura, myocardial infarction, peripheral embolism, symptomatic arterial desaturation, exacerbation of obstructive sleep apnea, hypoxemia out of proportion to the extent of lung disease, decompression sickness, altitude illness, and coronary artery spasm. This review paper will discuss the various PFO-associated conditions, relevant observational and prospective randomized trials, as well as preferred methods to make the diagnosis of a PFO.

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KEYWORDS Patent foramen ovale; cryptogenic stroke; paradoxical embolism; migraine; hypoxemic conditions

Introduction

Patent foramen ovale (PFO) is a common congenital cardiac lesion that has been associated with a host of clinical conditions, predominantly cryptogenic stroke and migraines. This brief review will go over the embryology, various clinical manifestations, diagnosis, and management of PFO and is a follow-up and complement to a similar work published in 2018.[1]

The fetal foramen ovale, necessary for fetal life, acts as a conduit for oxygenated blood to flow from the right atrium into the left atrium, thereby avoiding the non-aerated and highly resistant pulmonary circulation. Placental blood already has a low oxygen saturation of 67%. If the placental blood traversed the non-aerated pulmonary circulation, it would continue to lose oxygen and there would be insufficient oxygen for the fetal organs. The PFO is of existential importance, as demonstrated by its perseverance through evolution and presence in all mammals. At birth, two interrelated events occur: (1) right-sided heart pressures and pulmonary vascular resistance drop as pulmonary arterioles open secondary to oxygen filling the alveoli and (2) left atrium starts receiving blood preferentially from the lungs. These two mechanisms cause the flexible component of the PFO, the septum primum, to close and eventually fuse against the septum secundum. Complete fusion occurs by age 2 in about 75% of individuals, but patency persists in the remaining 20% and probe patency in another 5%. The reasons why the septa fail to close and produce a PFO are unknown but there is good evidence that genetic factors are involved.[2] Wilmshurst et al. studied the inheritance pattern of atrial shunts (PFO and atrial septal defects) by examining 71 relatives of 20 probands using contrast transthoracic echocardiography (TTE), and they concluded that the occurrence was consistent with autosomal dominant inheritance. Our data of 39 families consisting of 136 subjects suggest that PFO alone (i.e., no ASDs) is inherited in a non-Mendelian polygenic manner (unpublished). The presence of a Chiari network[3] and persistence of Eustachian valve[4] has also been hypothesized to predispose to patency of the foramen ovale.

The PFO is a residual tunnel-like defect with a variable anatomy, which has important implications in terms of PFO closure device choice and prognosis. One commonly used classification system identifies PFOs as either simple or complex.[5] A complex PFO has one or more of the following features – concomitant atrial septal aneurysm (ASA), Chiari network, eustachian valve, or hybrid defect, tunnel length ≥8 mm, multiple atrial septum fenestrations, septum secundum thickness >10 mm, and altered anatomy because of enlargement of the aortic root. The remaining PFOs are considered simple.

An ASA is an important feature to assess when evaluating a PFO because observational studies have found that it is more common in people who have a cryptogenic stroke and is associated with a higher rate of recurrent stroke.[6] Cabanes et al. reported that 33% (21/64) of patients with a cryptogenic stroke and PFO had an ASA, compared to 2% (1/50) of controls with a PFO.[6] The echocardiographic definition of an ASA is excursion of the septum primum from the midline plane of the atrial septum into either atrium by ≥10 mm or a combined (right plus left) excursion of ≥15 mm.

Discussion

PFO-mediated cryptogenic stroke

Cryptogenic stroke is a subtype of ischemic stroke without an identifiable cause despite guideline-directed evaluation. Initial

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observational studies demonstrated an association between cryptogenic stroke and PFO, with a higher prevalence of PFO, 44–66%, in patients with cryptogenic stroke, compared to 20% in the general population.[6,7] The frequency of PFO increased to 93% in patients with cryptogenic stroke who also had a history of migraine with frequent aura.[8]

This increased prevalence led to the hypothesis that PFO and cryptogenic stroke were causally related. Many influential neurologists were skeptical of this hypothesis because a high percentage of individuals with a PFO never experience a cryptogenic stroke. It is estimated that only 1 in 1000 (0.1%) people with a PFO develop a stroke per year. The issue of when to consider a PFO guilty and when to consider it an innocent bystander gave rise to the RoPE (Risk of Paradoxical Embolism) scale, which sought to assess the patient characteristics that made the PFO pathway a likely culprit for a paradoxical embolism as the cause of the stroke.[9,10] The RoPE score does not consider hypercoagulable state or PFO anatomy, both of which also contribute to the risk of stroke.[11,12]

The initial randomized controlled trials (RCTs) that evaluated the efficacy and safety of percutaneous PFO closure for the prevention of recurrent cryptogenic stroke were unable to demonstrate that PFO closure was superior to medical therapy.[13–15]

CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a PFO) enrolled 909 patients aged 18 to 60 years with a history of cryptogenic stroke or TIA and TEE-confirmed PFO.[13] Patients were randomized to a PFO closure arm (n = 447) with the STARFlex septal closure system (NMT Medical, Boston, Massachusetts, USA) followed by medical therapy consisting of aspirin 81 or 325 mg for 2 years and clopidogrel 75 mg for 6 months. Patients randomized to the medical therapy arm (n = 462) received either warfarin with a target international normalized ratio of 2.0 to 3.0, aspirin 325 mg daily, or warfarin plus aspirin 81 mg daily. The primary efficacy endpoint, a composite of stroke or TIA during 2 years of follow-up, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years, occurred in 5.5% (23/447) of patients in the PFO closure group and 6.8% (29/462) of patients in the medical therapy group (HR 0.78, 95% CI 0.45–1.35, p = 0.37). Inconsistencies between CLOSURE I and previous observational studies have been attributed to problems with the STARFlex septal closure device and enrollment of patients whose index stroke was unlikely secondary to paradoxical embolism.

The PC trial (Percutaneous Closure of PFO in Cryptogenic Embolism) enrolled 414 patients aged <60 years with a history of cryptogenic stroke, TIA, or extracranial peripheral thromboembolic event and TEE-confirmed PFO.[14] Patients randomized to the PFO closure arm (n = 204) underwent PFO closure with the Amplatzer PFO Occluder (Abbott, Chicago, Illinois, USA) followed by medical therapy consisting of aspirin 100–325 mg/day for ≥5 months plus either clopidogrel (75–150 mg/day) or ticlopidine (250–500 mg/day) for 1–6 months. Patients randomized to the medical therapy arm (n = 210) received an antithrombotic regimen that was left to the treating physician's discretion, with 57.1% (120) receiving aspirin, 16.7% (35) receiving a thienopyridine, 30.5% (64) receiving warfarin, and 2.4% (5) receiving no medications at discharge. The primary efficacy endpoint, a composite of death, non-fatal stroke, TIA, or peripheral embolism, occurred in 3.4% (7/204) of patients in the PFO closure group and 5.2% (11/210) of patients in the medical therapy group over a mean follow-up period of 4 years (HR 0.63, 95% CI 0.24–1.62, p = 0.34). Major limitations of the PC Trial included inadequate statistical power, inclusion of patients with extracranial systemic embolic events, and lack of blinding.

RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) enrolled 980 patients aged 18– 60 years with a history of cryptogenic stroke and TEE-confirmed PFO.[15] Patients assigned to the PFO closure arm (n = 499) underwent PFO closure with the Amplatzer PFO occluder and subsequently received aspirin 81–325 mg for 6 months plus clopidogrel for 1 month. Patients assigned to the medical therapy arm (n = 481) received one of five regimens: aspirin (46.5%), warfarin (25.2%), clopidogrel (14.0%), aspirin plus extended-release dipyridamole (8.1%), or aspirin + clopidogrel (6.2%). The primary efficacy endpoint, a composite of recurrent non-fatal ischemic stroke, fatal ischemic stroke, or early death, occurred at a rate of 0.66 events per 100 patient-years in the PFO closure group and 1.38 events per 100 patient-years in the medical therapy group (HR 0.49, 95% CI 0.22–1.11, p = 0.08) over a median follow-up of 2.1 years. Of note, the RESPECT trial was designed to assess outcomes after the occurrence of 25 events, and this occurred after a median of 2.1 years. Since the RESPECT trial almost met the primary efficacy endpoint, the Food and Drug Administration (FDA) agreed to extend the subject follow-up period. Over a median follow-up of 5.9 years, 18 events occurred in the PFO closure group, compared to 28 events in the medical therapy group (HR 0.55, 95% CI 0.31–0.999, p = 0.046).[16] One major limitation of the RESPECT trial was a difference in dropout rate between the PFO closure group (20.8%) and medical therapy group (33.3%). This resulted in unequal duration of exposure to the endpoint, thereby complicating interpretation of the results. Subsequent trials showed more convincingly that PFO closure was superior to standard of care medical therapy.[17–19]

CLOSE (PFO Closure or Anticoagulants vs. Antiplatelet Therapy to Prevent Stroke Recurrence) enrolled 663 patients aged 16–60 years with a history of cryptogenic stroke secondary to a PFO that was associated with an atrial septal aneurysm or large interatrial shunt.[17] Patients were initially split into three groups to determine if anti-platelet or anti-coagulant therapy was preferable if there was a contraindication to PFO closure. Group 1 (n = 524) consisted of patients with no contraindications who were randomized in a 1:1:1 fashion to PFO closure with 1 of 11 PFO closure devices plus long-term antiplatelet therapy (n = 173); antiplatelet therapy (n = 171); or oral anticoagulation (n = 180). Group 2 (n = 129) consisted of patients with contraindications to oral anticoagulation who were randomized to PFO closure (n = 65) or antiplatelet only (n = 64). Group 3 (n = 10) consisted of patients with

contraindications to PFO closure, who were randomized to antiplatelet only (n = 3) or oral anticoagulation (n = 7). Finally, the PFO closure and antiplatelet-only cohorts from groups 1 and 2 were combined and compared against each other whereas the oral anticoagulation and antiplatelet-only cohorts from groups 1 and 3 were combined and compared against each other. The primary efficacy endpoint, recurrent stroke, occurred in 0 patients in the PFO closure group and in 14 patients in the antiplatelet-only group after a mean follow-up of 5.3 ± 2.0 years (HR 0.03, 95% CI 0–0.26, $p < 0.001$). Similarly, recurrent stroke occurred in three patients in the anticoagulation group and in seven patients in the antiplatelet group after an approximate mean follow-up of 5.4 ± 2.0 years (HR 0.44, 95% CI 0.11–1.48), but statistical significance was not analyzed because the study was not adequately powered to compare outcomes in these groups. A limitation of CLOSE was slow patient recruitment, which resulted in premature termination of the study.

REDUCE (Gore Helex Septal Occluder/Gore Cardioform Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed Transient Ischemic Attack in Patients with PFO) enrolled 664 patients aged 18–59 years with a history of cryptogenic stroke and TEE-confirmed PFO.[18] Of note, patients with a history of traditional atherosclerotic cardiovascular disease risk factors that were uncontrolled, such as diabetes and hypertension, were excluded. Patients randomized to the PFO closure arm (n = 441) underwent PFO closure with the Gore Helex (39% of subjects) or Cardioform Septal Occluder (61% of subjects) (W.L. Gore and Associates, Flagstaff, Arizona). Patients randomized to the antiplatelet-only group (n = 223) received 1 of 3 regimens – aspirin, aspirin plus dipyridamole, or clopidogrel – and the choice was left to the discretion of the local investigator. The first coprimary efficacy endpoint, freedom from clinical evidence of an ischemic stroke through at least 24 months, occurred in 1.4% (6/441) of patients in the PFO closure group and in 5.4% (12/223) of patients in the antiplatelet-only group over a median follow-up of 3.2 years (HR 0.23, 95% CI 0.09–0.62, $p = 0.002$). The second co-primary efficacy endpoint, incidence of new brain infarction (clinical and silent) after 2 years of follow-up, occurred in 5.7% (22/383) of patients in the PFO closure group and in 11.3% (20/177) of patients in the antiplatelet-only group (RR 0.51, 95% CI 0.29–0.91, $p = 0.04$). Major limitations of REDUCE include lack of blinding, availability of off-label PFO closure devices, and differential dropout rates.

DEFENSE-PFO (Device Closure versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk PFO) enrolled 120 patients with a history of cryptogenic stroke and high-risk PFO (defined as the presence of an ASA, hypermobility, or PFO height ≥2 mm on TEE).[19] Patients randomized to the PFO closure arm (n = 60) underwent PFO closure with the Amplatzer PFO occluder and subsequently received antiplatelet therapy. Patients randomized to the medical therapy arm (n = 60) received either antiplatelet therapy or anticoagulation therapy. The specifics of the medical therapy, including type and duration, were left to the discretion of the local investigator. The primary efficacy endpoint, a composite of stroke, vascular death, or Thrombolysis in Myocardial Infarction (TIMI)-defined major bleeding, occurred in 0% of patients in the PFO closure group and in 10% (6/60) of patients in the medical therapy only group over a median follow-up of 2.8 years (95% CI 3.2–22.6, $p = 0.013$). A major limitation of DEFENSE-PFO was early termination secondary to concerns regarding patient safety.

Discrepancy between the early RCTs (CLOSURE I, PC Trial, and RESPECT early follow-up) and newer RCTs (RESPECT long-term follow-up, CLOSE, REDUCE, and DEFENSE-PFO) can be explained by the utilization of different study populations and length of follow-up. A retrospective application of the RoPE score to the earlier RCTs revealed that a wide range of RoPE scores were included, implying that the statistically insignificant results might have been due to inclusion of patients with cryptogenic stroke unrelated to PFO who were unlikely to show a benefit from PFO closure rather than a failure of treatment.[20]

Risk factors and certain anatomical features (ASA or large shunt), for a PFO-associated stroke, have been identified, such as a prothrombotic state (birth control pill use) and transient elevation of right atrial pressure (Valsalva maneuver). Kar et al. retrospectively looked at 79 female patients with a history of cryptogenic stroke, TIA, or peripheral arterial embolism who were referred for percutaneous PFO or ASD closure, and found that 66% (52) were taking oral contraceptive pills or hormonal replacement therapy at the time of their event.[21] The impact of stopping these estrogen-based prothrombotic medications on the risk of recurrent stroke is unclear. Including these subjects in the various RCTs, once the medications were stopped after the stroke, could have reduced the frequency of recurrent stroke in the medical arm, thereby making it more difficult to demonstrate a benefit with PFO closure.

One meta-analysis combining the six cryptogenic stroke RCTs confirmed that percutaneous PFO closure, compared to medical therapy, reduced risk of recurrent stroke (RR 0.41, 95% CI 0.21–0.82, $p = 0.012$) but not TIA (RR 0.78, 95% CI 0.53–1.14, $p = 0.211$) and increased risk of new-onset transient atrial fibrillation/flutter (RR 3.95, 95% CI 2.08–7.50, $p < 0.001$).[22] Other meta-analyses reported similar findings.[23–26] Ntaios et al. showed that ischemic stroke recurrence in the percutaneous PFO closure group was less than half that of the medical therapy group (0.53 vs. 1.1 per 100 patient-years, OR 0.43, 95% CI 0.21–0.90, RRR 51.5%, ARR 2.1%, NNT 46.5 for 3.7 years.[24]

In the United States, the Amplatzer PFO Occluder (Figure 1a) and Gore Cardioform Septal Occluder (Figure 1b) are approved by the Food and Drug Administration for patients predominantly aged 18–60 years with a cryptogenic stroke, which is thought to be PFO-mediated as diagnosed by a neurologist.[27,28]

PFO-mediated myocardial infarction

Coronary embolism, an important non-atherosclerotic cause of acute myocardial infarction (MI), has a prevalence of 2.9%.[29] The three types of coronary embolism are direct (atrial fibrillation), paradoxical (PFO or pulmonary arteriovenous malformation), and iatrogenic (during coronary angiography and intervention), with direct being the most common. The true prevalence of paradoxical coronary embolism is difficult to estimate because this type of embolic-

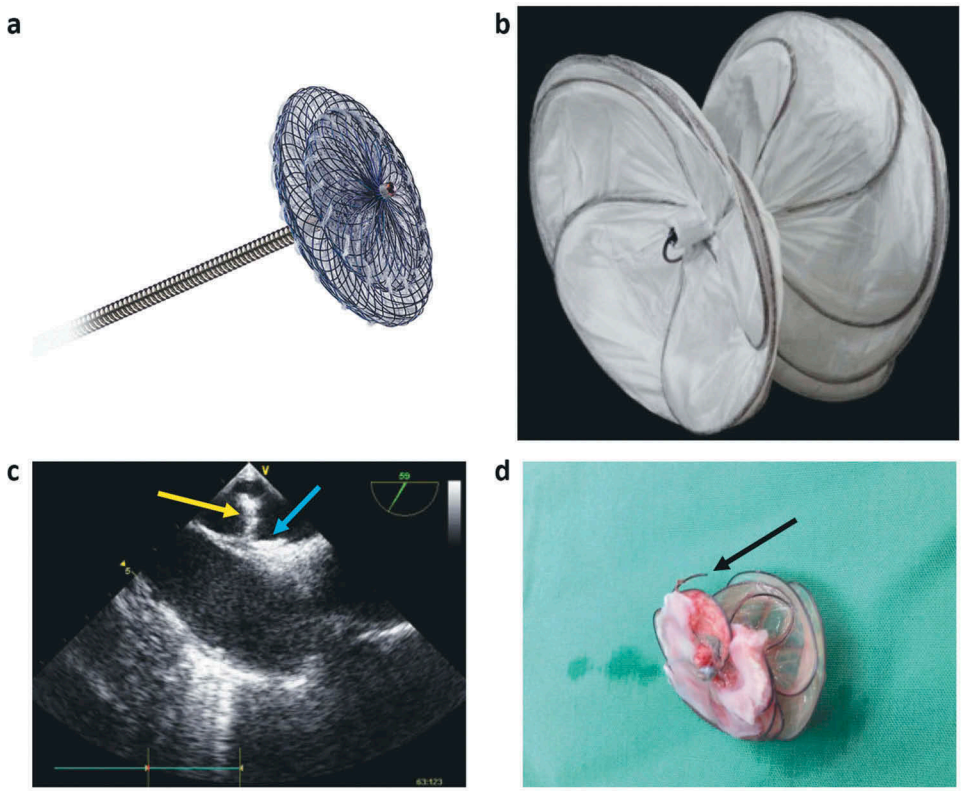

Figure 1. PFO closure devices and associated complications. (a) and (b) Depictions of the FDA-approved PFO closure devices Amplatzer PFO Occluder (a) and Gore Cardioform Septal Occluder (b). (c) Thrombus formation (yellow arrow) found on a CardioSEAL device (light blue). (d). A postoperative picture of the Gore Helex Septal Occluder showing one wire frame fracture (black arrow). PFO = patent foramen ovale. FDA = Food and Drug Administration. *A – courtesy of Abbott. B – courtesy of W.L. Gore & Associates Inc. D – reprinted from ref 74.*

mediated MI is rarely considered, especially when other possible causes of MI are present. However, paradoxical coronary embolism has been documented in the form of case reports in children,[30] adults,[31,32] the elderly[33] and cohort studies.[29,34]

The probability for an MI to be PFO-mediated is dependent on many characteristics, including age, number of traditional cardiovascular risk factors present, number of thromboembolic risk factors present, and angiography results. Consequently, it is possible to see PFO-mediated MI in the young and old. Angiographically, a paradoxical embolus to a coronary artery appears as a cutoff sign and needs to be distinguished from spontaneous coronary artery dissection.

The initial management of paradoxical coronary embolism, similar to acute coronary syndrome from atherosclerosis, consists of emergent coronary angiography. The proceduralist should consider aspiration thrombectomy if there is a large thrombus burden since it reduces the amount of thrombotic material that may embolize to the distal part of the coronary circulation, permits histological assessment that can help determine the origin of the thrombus[35], and may provide a better assessment of the coronary anatomy once the thrombus is removed. After successful acute coronary revascularization, an embolic source should be sought, including PFO screening with agitated saline bubble study or right heart catheterization. If a PFO is found, PFO closure should be considered.

PFO-mediated peripheral embolism

Paradoxical peripheral embolism is a less common type of peripheral embolism than direct embolism, but it can still result in dangerous acute limb ischemia. In a series of 406 patients with peripheral emboli, the source of embolus was cardiac in 61%, arterio-arterial in 15%, probable paradoxical embolism in 2%, possible paradoxical embolism in 2%, and unknown in 20%.[36]

Although PFO-associated stroke is the most common type of PFO-mediated embolic event, several studies describe PFO-mediated noncerebral paradoxical events as well. Inglessis et al. assessed the frequency of indications for transcatheter PFO closure and found that 3% underwent PFO closure for peripheral embolism.[37] Dao et al. conducted a similar study and also found that 3% of patients presented with peripheral embolism as the index event.[38] It is unclear why the majority of PFO-mediated paradoxical embolism cases present as strokes. Cerebral blood flow is 750 mL/minute, which is three times the blood flow to the coronary arteries. One would predict that there would be one myocardial embolism for every three strokes, but the reported incidence is less than that. One hypothesis is that the brain is more susceptible to small emboli than the rest of the body (i.e., the remainder of the systemic circulation also experiences paradoxical embolic events, but these events are clinically asymptomatic and hence under-diagnosed).

Patients presenting with PFO-mediated peripheral embolism are initially managed in the same manner as those presenting with acute limb ischemia. After successful treatment, evaluation for a cardioembolic source, large vessel atherosclerosis, and PFO should be undertaken.

PFO and migraine

The prevalence of PFO is higher (50%) in people who have migraine with aura than in the general population (20%) and even higher in people with both cryptogenic stroke and migraine (79%).[8] Aura is comprised of a transient neurologic deficit that can occur before, during, or after the headache, and commonly presents as a visual defect, such as a scintillating scotoma or fortification spectra. Current evidence suggests that migraine with aura is the result of cortical spreading depolarization, and it may be triggered by hypoxia, ischemia, or emboli without ischemia.[39] In patients with right-to-left shunts (RLS), vasoactive substances such as serotonin or platelet emboli may bypass the lungs and trigger cortical spreading depolarization and subsequently elicit migraine with aura.[40]

A 2016 meta-analysis of case–control studies assessing the association of migraine and PFO found that patients with PFO had a significantly higher prevalence of migraine with aura (OR 3.36, 95% CI 2.04–5.55, $p < 0.00001$) and migraine with and without aura (OR 2.46, 95% CI 1.55– 3.91, $p = 0.0001$) but not migraine without aura (OR 1.30, 95% CI 0.85–1.99, $p = 0.22$).[41] Despite these observations and a higher PFO prevalence in migraineurs compared to non-migraineurs,[42,43] the three RCTs that assessed the efficacy and safety of PFO closure in patients with migraine with aura and/or migraine without aura failed to show that PFO closure was superior to medical therapy[44,45,46]. Discrepancy between the observational studies and RCTs can be explained by a high prevalence of residual RLS post-PFO closure (MIST), lack of power due to incomplete enrollment (PRIMA), and significant placebo (Hawthorne) effect (PREMIUM).

Two study-level meta-analyses of the three RCTs and 1 patient-level pooled analysis of PRIMA and PREMIUM showed that PFO closure was significantly superior to medical therapy in reducing migraine attacks and days.[47–49] Furthermore, Sommer et al. described that 90/136 patients with migraine with or without aura and PFO had ≥50% reduction in headache days following adequate platelet inhibition with a P2Y12 inhibitor. Among 56/90 patients who subsequently agreed to undergo PFO closure with thienopyridine discontinuation after 3 months, 52/55 (94%) reported ongoing migraine relief, with a follow-up range to 6 years.[50] This hypothesis will be tested in the upcoming RELIEF Migraine-PFO trial, a RCT that will attempt to identify those migraineurs with a PFO who are more likely to respond to PFO closure based on their response to thienopyridines. The thienopyridine responders will then be randomized to PFO closure or a sham procedure.

PFO and hypoxemic conditions

In patients with no underlying pulmonary disease, the left atrial pressure is 5–7 mm Hg higher than the right atrial pressure. This pressure gradient is reversed in patients with pulmonary disease, such as chronic obstructive pulmonary disease, due to an increase in pulmonary artery pressure. In patients with pulmonary disease and a concomitant PFO, reversal of the normal inter-atrial pressure gradient could result in an increased volume of deoxygenated blood shunted from the right atrium to the left atrium, resulting in hypoxemia out of proportion to the underlying pulmonary disease. One proposed method to quantify the contribution of hypoxemia from a PFO to the overall hypoxemia is to measure arterial oxygen saturations before and after balloon occlusion of the PFO. There are several case series suggesting that selected patients with hypoxemia and COPD may benefit by PFO closure with increased oxygen saturation.[51,52]

The most common hypoxemic condition potentially related to PFO is obstructive sleep apnea (OSA). Several observational studies have demonstrated a higher prevalence of PFO in patients with OSA compared to the general adult population. Shanoudy et al. conducted a single-center case–control study (n = 72) to assess the prevalence of PFO and its contribution to hypoxemia in patients with OSA. They discovered that the OSA group (n = 48), compared to the control group (n = 24), had a significantly higher prevalence of PFO (69% vs. 17%, $p < 0.0001$) and lower systemic oxygen saturations with Valsalva provocation (−2.4% ± 1.5% vs. 1.3% ± 0.6%, $p = 0.007$).[53] Mojadidi et al., in a similarly designed study, also showed that the OSA group (n = 100), compared to the control group (n = 200), had a higher prevalence of right-to-left shunt (42% vs. 19%, $p < 0.0001$) as well as a higher oxygen desaturation index (ODI)/apnea-hypopnea index (AHI) ratio (0.85 ± 0.07 vs. 0.68 ± 0.04, $p < 0.0001$), a metric for quantifying the severity of hypoxemia relative to the degree of OSA.[54] These findings suggest that PFO closure could be a potential treatment for patients with OSA who also have a PFO. Rimoldi et al. compared the change in ODI and AHI pre- and post-PFO closure in patients with OSA and PFO to patients with OSA without PFO, and discovered that the PFO closure group, compared to the control group, demonstrated significant reductions in both indices (Δ AHI = −7.9 ± 10.4 vs. +4.7 ± 13.1 events per hour, $p = 0.0009$; Δ ODI = −7.6 ± 16.6 vs. +7.6 ± 17.0 events per hour, $p = 0.01$).[55] The authors concluded that in patients with OSA and PFO, percutaneous device closure improves sleep-disordered breathing and nocturnal oxygenation. On the contrary, Hoole et al. were unable to replicate these findings. One potential reason for the discrepancy may be the use of a TTE bubble study to make the diagnosis of PFO, which has a lower sensitivity compared to transesophageal echocardiogram (TEE) or transcranial Doppler (TCD).[56,57]

A second hypoxemic condition related to PFO is platypnea-orthodeoxia syndrome (POS). Given the low prevalence of this syndrome, data on POS and its association with PFO and the benefit of PFO closure are limited to case series and observational studies, all of which show improvements in mean arterial oxygen saturation. Landzberg et al. published a case series of eight patients with POS and PFO demonstrating that PFO closure improved oxygen saturations (83% ± 3% prior to closure to 93% ± 2% following PFO closure).[58] Shah et al. reported similar findings (n = 52, pre-PFO closure

oxygen saturation = 81 ± 8%, post-PFO closure procedure oxygen saturation = 95.1 ± 0.5%).[59] Guerin et al., in the largest observational study to date looking at PFO closure in patients with PFO and POS (n = 78), assessed oxygen saturation and dyspnea severity pre- and post-PFO closure, and they reported significant improvements in both outcomes (change in O_2 saturation = from 84.6 ± 10.7% to 95.1 ± 6.4% ($p < 0.001$) and change in dyspnea grade = from 2.7 ± 0.7 to grade 1 ± 1 ($p < 0.001$)).[60]

Two other PFO-related hypoxemic conditions are associated with altitude elevation: acute mountain sickness (AMS) and high-altitude pulmonary edema (HAPE). West et al. showed through a single-center, prospective, observational study of hikers climbing Mount Whitney, California (14,500′) that the prevalence of PFO was higher in people who developed AMS compared to hikers without AMS (15/24 (63%) vs. 44/113 (39%), $p = 0.034$) with the adjusted odds ratio for developing AMS in the presence of PFO, compared to the absence of PFO, of 4.15 (95% CI 1.14–15.05, $p = 0.03$).[61] Similarly, Allemann et al. reported that professional mountain climbers who had a history of HAPE, a potentially life-threatening consequence of worsening AMS, had a higher prevalence of PFO compared to those who did not (69% vs. 16%, $p = 0.001$).[62]

Since the data published on PFO closure for hypoxemic conditions are based on observational studies, current society guidelines do not recommend percutaneous PFO closure as a therapy for these conditions. However, RCTs such as the ongoing PFO Closure for Obstructive Sleep Apnea (PCOSA-1; NCT 02771561) trial in the United Kingdom might change that.

PFO and decompression illness

Decompression illness occurs when venous bubbles, which form from inert nitrogen gas dissolved within tissues as they are liberated secondary to a drop in ambient pressure as the diver ascends, overwhelm the pulmonary filtration system or reach the arterial circulation directly, such as in the presence of a PFO. Torti et al. demonstrated that divers with a PFO, compared to divers without a PFO, had a significantly higher prevalence of ≥1 major decompression illness event (18/63 (29%) vs. 10/167 (10%), $p < 0.001$), with a relative risk of 4.8 (95% CI 2.3–10.1).[63] One particular area of interest in patients with decompression illness events is occurrence of white matter lesions, which are thought to represent silent ischemic damage. It is reported that decompression illness events result in white matter lesions, but there is conflicting evidence whether the frequency of white matter lesions is exacerbated by the presence of PFO. Schwerzmann et al. found that divers with a PFO, compared to divers without a PFO, were 4 times more likely to develop decompression illness (RR 4.5, 95% CI 1.2 to 18.0, $p = 0.03$), consistent with Torti et al., and had twice the number of white matter lesions (1.23 ± 2.0 vs. 0.64 ± 1.22 white matter brain lesions per person, $p = 0.07$).[64] On the contrary, Gerriets et al. found that among divers with TCD-proven RLS, 0/16 (0%) had white matter lesions although 3/15 RLS+ divers demonstrated post-dive arterial gas emboli without any pathologic findings on brain magnetic resonance imaging.[65]

PFO and coronary artery spasm

Coronary artery spasm is a well-recognized cause of myocardial infarction, but the pathogenesis is unclear. One proposed mechanism is that a PFO could expose the arterial circulation to vasoactive substances (e.g., serotonin) to which it otherwise would not be subjected. Several manuscripts support this hypothesis by demonstrating coronary artery spasm on angiography with vasospastic angina that is relieved when the PFO is closed. Bourgault et al. described a 60-year-old man with stable coronary artery disease and a PFO who developed coronary spasm secondary to serotonin secreted by a carcinoid tumor.[66] Dao and Tobis described a 49-year-old woman with a history of intermittent chest pain, migraines, and PFO who had normal coronary arteries on angiography and intravascular ultrasound but had angiographic documentation of coronary spasm associated with ventricular fibrillation. Both the chest pain and migraines resolved following PFO closure.[38]

Similar to PFO with hypoxemic conditions, PFO with decompression illness and PFO with coronary artery spasm are limited to observational studies, and RCTs are needed to prove a causal relationship.

Diagnosis and imaging of PFO

A number of ultrasound-based diagnostic imaging modalities – transthoracic echocardiogram (TTE), transcranial Doppler (TCD), and transesophageal echocardiogram (TEE) – can be utilized to detect and quantify a PFO. However, the gold standard for diagnosing a PFO is right heart catheterization with visualization of a guidewire crossing the atrial septum during fluoroscopy. A standard J-wire might not easily cross small PFOs because the diameter of the wire is larger than the opening of the PFO. In these cases, we perform a hand injection of contrast for visual confirmation of the right-to-left shunt. If the probe patent PFO is >1 mm, the proceduralist can usually get a straight wire or a multipurpose catheter by itself to go across the PFO. However, probe patent PFOs are too small to be clinically relevant and should not be closed. Echocardiographic studies that do not use a right heart catheterization as the standard tend to underestimate the frequency of PFO, leading to misidentification of some subjects.

TTE with agitated saline bubble study is the most commonly used imaging modality to screen for a PFO as it is noninvasive and readily available. However, it has the lowest sensitivity. A meta-analysis of 15 prospective studies (n = 1995 patients) reported that TTE with harmonic imaging had a sensitivity of 90.5% and specificity of 92.6% when compared with TEE as the reference.[67]

The TCD bubble study has gained traction over the past few years as the imaging modality of choice for detection of a PFO given its high sensitivity, low cost, good safety profile, and tolerability. One large meta-analysis of 27 prospective studies (n = 1968 patients) reported that a TCD bubble study had a sensitivity of 97% and specificity of 93% for the detection of intracardiac right-to-left shunt when compared with TEE as the reference.[68]

TEE with bubble study yields direct visualization of the atrial septal anatomy, with the ability to identify an atrial septal aneurysm, eustachian valve, and Chiari network, and most physicians therefore consider it as the reference standard for detecting a PFO. However, a meta-analysis comparing TEE to PFO confirmed by surgery, right heart catheterization, or autopsy found that TEE had a weighted sensitivity of 89% and specificity of 91%. This implies that TEE misses or misdiagnoses 10% of PFOs.[69] Furthermore, since a PFO remains closed most of the time, TEE, compared to a sizing balloon, significantly underestimates the potential PFO size.[70] The larger the stretched PFO size by sizing balloon, the greater the PFO size underestimation by TEE. This is because gentle inflation of the sizing balloon opens the PFO to its maximal anatomical size and shape. Consequently, there is no justification to state that a PFO is "too small" to be the cause of a given stroke based solely on echocardiography.

In institutions where TCD is available, a TCD bubble study should be utilized as the initial screening test to identify and quantitate the presence of a right-to-left shunt. A TEE is then used to confirm the presence of a PFO versus a pulmonary arteriovenous malformation and to assess for any other cardiac pathology.

PFO closure

Symptomatic PFOs can be closed either percutaneously or surgically. The initial PFO closure procedures were performed surgically and required cardiac bypass. However, with the introduction of percutaneous techniques, a shift in practice occurred to remove the risk and complications of open-heart surgery or bypass. Currently, the most common indication for surgically closing a PFO are removal of a percutaneously placed PFO closure device due to a history of device-induced complication (e.g., arrhythmia, embolization, erosion, tamponade) and nickel allergy. This procedure can be done robotically without placing the patient on bypass. The upcoming Stitch Closure of PFO and Septal Repair (STITCH) trial will compare the safety and effectiveness of the NobleStitch EL suture-based closure system to the Amplatzer PFO Occluder.

Percutaneous PFO closure, generally considered an outpatient procedure, is performed under light sedation with use of either intracardiac echocardiogram or TEE. Although the type of closure device used and post-PFO closure medical therapy are operator dependent, the most commonly used devices are the Amplatzer PFO Occluder and Gore Cardioform Septal Occluder and the most common post-PFO closure medical therapy is aspirin 81 mg/day plus clopidogrel 75 mg/day of varying duration followed by aspirin alone. One issue regarding post-PFO closure medical therapy is which patients should be placed on antiplatelet therapy versus on anticoagulation. Patients remain at risk for developing thromboembolic events even after a PFO is closed. Since there are no RCTs comparing antiplatelet therapy versus anticoagulation following PFO closure, the decision is left to the treating physician.

While PFO closure is effective, quick, minimally invasive, and performed on an outpatient basis, it is not without risk. Merkler et al. assessed safety outcomes of percutaneous PFO closure in 1887 patients who underwent the procedure within a year of cryptogenic stroke or TIA.[71] The investigators discovered that the rate of any adverse outcome, defined as atrial fibrillation or flutter, cardiac tamponade, pneumothorax, hemothorax, vascular access complication, or death, during the hospitalization for PFO closure was 7.0% (95% CI 5.9–8.2%). This rate varied with age: 10.9% (95% CI 8.6–13.6%) in patients >60 years of age, compared to 4.9% (95% CI 3.8–6.3%) in patients ≤60 years of age. The most common adverse event was atrial fibrillation/flutter, which occurred at a rate of 3.7% (2.9–4.6%).

Our group evaluated residual shunt rate, a metric of the technical success of PFO closure, and complications associated with six different PFO closure devices – Amplatzer ASO (n = 17), Amplatzer Cribriform (n = 14), Amplatzer PFO (n = 33), Cardioform (n = 104), CardioSEAL (n = 14), and Helex (n = 137) – and found that the Cardioform device had the highest rate of effective closure (100%) but also the highest rate of transient atrial fibrillation (13%).[72] On the contrary, Hornung et al. reported that, among the Amplatzer (n = 220), Helex (n = 220), and CardioSEAL-STARFlex (n = 220) devices, the Helex device had a high rate of effective closure (96.8%) but also the lowest rate of atrial fibrillation (2.3%).[73] These opposite findings are most likely secondary to utilization of different follow-up methods. Gevorgyan et al. used the more sensitive TCD method to assess residual shunt following PFO closure, whereas Hornung et al. used TEE.

While atrial fibrillation is widely recognized as the most common adverse event associated with PFO closure, thrombus formation on the PFO closure device (Figure 1c) and life-threatening complications, such as cardiac tamponade (Figure 1d), have also been reported.[73,74] These complications can occur even a few years after the procedure, and it is therefore critical that physicians be aware of them so that they can be recognized promptly, thereby expediting treatment.

Conclusions

PFO, once regarded as a mostly benign heart defect, is now recognized to be associated with numerous medical conditions, including death, paradoxical embolism resulting in stroke, myocardial infarction, peripheral ischemia, migraine with aura, hypoxemia, decompression illness, and coronary artery spasm. This brief review discussed the evidence associating PFO and the various clinical conditions, and a more thorough discussion can be found in the book titled *Patent Foramen Ovale (PFO) Closure for Stroke, Myocardial Infarction, Peripheral Embolism, Migraine, and Hypoxemia*.[75] Despite many observational studies and nine completed RCTs that contribute to our understanding of PFO, many uncertainties, such as the genetic basis of PFO, molecular consequences of RLS through a PFO, role of PFO closure in patients <18 years and >60 years old, role of PFO size in PFO-associated conditions, impact of device-induced atrial fibrillation, and outcome differences between different PFO closure devices, still exist. The current percutaneous closure devices are not without risk, which underscores the need for developing safer devices. These issues highlight the need for further research in this field.

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