Title

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CHAPTER

18

The Full Spectrum of PFO: Are We Seeing Just the Tip of the Iceberg?

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OUTLINE

CLINICAL CASE

A 41-year-old man was referred for consideration of percutaneous closure of his patent foramen ovale (PFO). The patient had a recent stroke with temporary expressive aphasia and right hand numbness. Magnetic resonance imaging (MRI) confirmed a left-sided parietal stroke, and there was no carotid dissection or atherosclerosis. Although PFO closure was planned in 2017 due to a high RoPE score of 8 (84% chance that stroke was from the PFO, 6% risk of 2-year stroke recurrence), the insurance company denied it despite multiple appeals. A subsequent event monitor showed that with peak exertion of riding his bicycle, he developed transient atrial fibrillation. Given his young age and absence of other comorbidities, it was deemed unlikely that the transient atrial fibrillation could have caused a thrombus in the left atrial appendage resulting in stroke; paradoxical embolism continued to be the predominant suspected culprit of stroke. In support of this, an MRI venogram revealed proximal and distal compression of his left iliac vein by the left common iliac artery, consistent with May-Thurner syndrome. There was no evidence for deep venous thrombosis and no clinical leg swelling; thus, the left iliac vein was not stented. He was prescribed apixaban 5 mg twice daily.

One year after his initial stroke, the patient presented with nystagmus and dysconjugate gaze; he had a second stroke involving the basilar artery with MRI-confirmed infarction of the pons territory. Diagnosed too late, he was not treated with lytic therapy, but his symptoms fortunately resolved. The recurrent stroke occurred with full medical compliance on apixaban therapy. His neurologist recommended PFO closure. By that time, based on updated recommendations from the Food and Drug Administration of the United States, the insurance companies had altered their reimbursement guidelines and authorized payment for a percutaneous PFO closure procedure. Paroxysmal atrial fibrillation, again, seemed an unlikely culprit because he was on oral anticoagulation at the time of the recurrent stroke. His cardiologist concluded that apixaban was not completely effective against a potential venous thrombus that likely passed through the PFO and resulted in paradoxical embolism. Finally, the question remained whether the left iliac vein compression was the source of venous thrombosis, despite a clinically and probably insignificant May-Thurner syndrome with absence of proven deep vein thrombosis. The patient was referred

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for atrial fibrillation ablation, followed by percutaneous PFO closure during which a left femoral venogram was recommended.

THE FULL SPECTRUM OF PFO [1]

A PFO is present in about 25% of the population [2]. Once regarded as a benign anatomical variation, right-to-left shunting across a PFO has now been recognized to be associated with a wide range of pathologies and clinical syndromes. From paradoxical embolism engendering death, stroke, myocardial infarction, and peripheral ischemia, to its role in chronic and debilitating conditions such as migraine headache with aura and hypoxemia [3–6], the PFO maintains its uniqueness among congenital heart defects by choosing to remain clinically silent until it causes serious trouble.

The ease and safety profile place percutaneous PFO closure among the most practicable interventional cardiology procedures, with robust long-term clinical yield. Yet, after its introduction in 1992, PFO closure was met with little enthusiasm and largely ignored for more than 2 decades [7]. The early randomized trials of PFO closure for stroke fell short of statistical significance, in part due to low-risk patient selection, limited follow-up, and the shortcomings of intention-to-treat analyses (Chapter 6) [8–10]. Subsequent meta-analyses of these trials, which showed greater efficacy and excellent safety of PFO closure over medical therapy for prevention of recurrent stroke, did little to impress the skeptics and change respective stroke guidelines [11]. They continued to advise against PFO closure although it had long been proven at least noninferior and deserved to be offered as an attractive alternative to lifelong blood thinners. The long-term follow-up of the largest randomized trial [12] was the first to show a statistically significant reduction of recurrent stroke events, even in the intention-to-treat cohort. It is puzzling that a *P*-value that had just descended from formerly .08 in the first publication [10] to .046 [12] suddenly caught everyone's attention. The positive effect of PFO closure was achieved despite the presence of 3 patients randomized to the closure arm who had recurrent stroke, counted as stroke after PFO closure, although they did not actually receive a device. Recently, 3 additional randomized trials [13–15] and their meta-analyses [16–18] have unequivocally established PFO closure's superiority over standard of care blood thinners for secondary prevention of stroke, in patients with a PFO-associated stroke (Chapter 7). These trials have also expanded our understanding of stroke patients with high-risk PFOs; randomized and nonrandomized studies have shown an even higher clinical yield when PFO closure was performed for patients with high-risk echocardiographic features (atrial septal aneurysm, septal hypermobility, Eustachian valve, Chiari network, or major shunt through a large PFO). As an example, the number needed to treat (NNT) in the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial, to prevent 1 stroke at a 5-year follow-up, was estimated to be 42 [12]; in comparison, a subanalysis of the final RESPECT trial results (median follow-up 5.9 years) showed a very low NNT when PFO closure was performed for stroke patients with an atrial septal aneurysm (NNT = 16) or large shunt (NNT = 20) (*P*-interaction = .04 for both) [12]. The DEFENSE-PFO (Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk PFO) and CLOSE (PFO Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence) trials, studies that only included patients with high-risk PFOs, remarkably demonstrated zero recurrent strokes in the device arm at 2 and 5 years respectively (NNT = 10 and 20, respectively) [13,15]. Such a therapeutic achievement has yet to be observed even with the strongest anticoagulant, not to mention the 2%–4% annual risk of bleeding associated with oral anticoagulation that increases with age. From a pathophysiologic standpoint, it makes sense that high-risk PFOs are more dangerous. A large PFO exhibits more right-to-left shunting, an atrial septal aneurysm opens the PFO with virtually every heartbeat, and a Eustachian valve or Chiari network guide thrombi from the inferior vena cava straight to the PFO opening. A positive result in the randomized trials, even in the presence of some residual right-to-left shunting post-PFO closure, suggests that the device may act as a filter even when the PFO is not completely sealed [12,14]. It is hypothesized that this may not be the case with suture closure of a PFO. Now that the characteristics have been identified that make a PFO dangerous, is there a role of PFO closure for primary prevention in those patients, particularly if they are also at high risk for venous thromboembolism? Screening and investigating patients who are undergoing major surgery [19] or those with deep venous thrombosis or pulmonary embolism [20,21] would be a good place to start looking.

The prevalence of paradoxical embolism from a PFO is underestimated in clinical medicine. Other identified causes are usually blamed first, such as ruptured atherosclerotic plaque, spontaneous cerebral or coronary dissections, or atrial fibrillation. The PFO may be the first culprit identified, but it is the last one blamed. This is as illogical as the following analogy. The police are informed about a burglary in the village. They ignore the burglar called PFO sitting right in front of the police station but rather swarm out to painstakingly round up all other notorious local

burglars and check their alibis. They are all clean. Only then, the police take in the easiest to apprehend burglar called PFO. Perhaps this is because it is common to incidentally find a PFO in adults, but is that not equally the case for atrial fibrillation in the elderly [22]? We do not hesitate to place atrial fibrillation patients on oral anticoagulation, despite the annual bleeding risk of anticoagulants and knowing that some atrial fibrillation patients may never have a stroke without anticoagulation. Despite a better efficacy and safety profile than oral anticoagulants, and absent concern for compliance of taking a pill a day, PFO device closure is used as a last resort only if no other stroke causes exist. Is it because PFO closure is a remunerated procedure done by cardiologists rather than a pill a day prescribed by any doctor? The notion that a PFO cannot cause a stroke in the presence of another cause of stroke is counterintuitive; no medical condition is treated this way. For example, if an ischemic stroke patient presents with both atrial fibrillation and carotid disease, do we treat the carotid stenosis and ignore the atrial arrhythmia? The inaccurate assumption that the PFO is the culprit only in the absence of other culprits makes paradoxical embolism an underestimated and underdiagnosed entity in real life. Furthermore, considering that the coronary to cerebral blood flow ratio is 1:3 (220 vs. 750 mL/min), 1 right-to-left shunt-mediated myocardial infarction per 3 right-to-left shunt-mediated cerebral ischemic events makes more sense than the estimated 1:100,000 incidence reported in the literature. One large 20-year cohort study found a high rate of coincidental strokes and myocardial infarctions among patients presenting with acute pulmonary embolism [23]. Despite the fact that the literature had already established PFO as a culprit for simultaneous embolisms in the systemic and pulmonary circulations [20], PFO was inexcusably not mentioned in the paper [23] or the accompanying editorial [24]. More recently, this has been rectified as the literature continues to prove a higher incidence of ischemic strokes in symptomatic pulmonary embolism patients who have a PFO, when compared to those with no PFO [22,25].

Based on a large autopsy study, the prevalence of PFO decreases from 34% during the first 3 decades of life to 25% during the fourth to eighth decade, and then 20% thereafter [2]. This observation must be accounted for by either spontaneous PFO closure later in life or selective mortality (lower life expectancy of PFO carriers). However, there have been no reports of transesophageal echocardiography–documented spontaneous closure of a PFO over time. Most people with a PFO will remain asymptomatic for life. Yet, since the early initial report of a young woman who died of a PFO-mediated stroke by Julius Cohnheim in 1877 [26], the potential of the PFO pathway to kill has been apparent and was corroborated when comparing mortality in PFO carriers with and without device closure

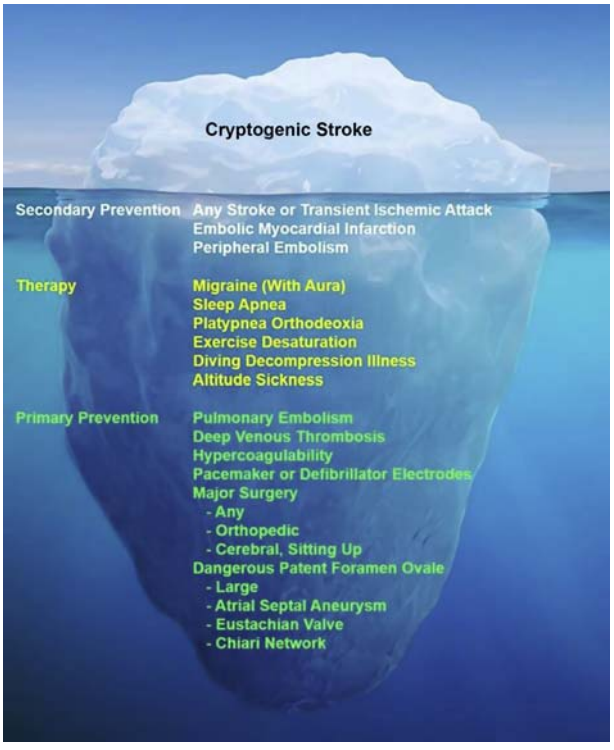

FIGURE 18.1 Established indication (visible tip of the iceberg) and plausible indications (invisible body of the iceberg) for device closure of the PFO. *Adapted with permission from Ref. [1].*

[27]. Our understanding of PFOs and high-risk PFOs has increased over time, along with improved technique, ease, and safety of device closure. Percutaneous PFO closure is now accomplished easily as a same-day procedure with minimal discomfort and risk. Patients can go back to their usual routine the same day, and posttreatment usually consists of a few months of low-dose acetylsalicylic acid. Postclosure atrial fibrillation/flutter occurs in about 5% of procedures [16–18]; however, these arrhythmias are usually early, transient, and they rarely cause stroke or need any, let alone long-term, anticoagulation. Of all patients randomized to a device in the cryptogenic stroke trials, 0.1% had recurrent stroke presumed to be from device-associated atrial fibrillation [28,29]. The 4 statistically positive PFO closure trials showed a NNT of 10–42 to prevent 1 stroke in 2–5 years [12–14]; it has been previously extrapolated that the NNT may be as low as just 2 PFOs closed to prevent 1 stroke with a lifelong follow-up [30]. With a cost generously estimated at $10,000–$20,000, procedural simplicity, excellent efficacy and safety, PFO closure for stroke seems like a no-brainer (pun intended).

Paradoxical embolism causing stroke, myocardial infarction, or peripheral embolism is only part of the story. PFO closure reduces the frequency and duration of migraine with aura [4,5]; can make it safer to live or climb in high altitude [31], dive [32,33], undergo major surgery [19]; and improves hypoxemia from sleep apnea [34,35], platypnea-orthodeoxia [36], and exercise desaturation [6,37]. Moreover, PFO closure for one indication provides a collateral benefit for the other indications, all at the same cost. A migraineur treated with PFO closure gets lifelong protection from paradoxical embolism and PFO-mediated hypoxemia, and vice versa. Despite a multitude of observational studies on PFO closure, 9 completed randomized trials, and more ongoing trials, we are seeing just the tip of the iceberg (Fig. 18.1) [1]. With this in mind, it is time to stop calling it an "innocent bystander" and reclassify the PFO for what it really is: the most common congenital defect in the world, with a license to kill [1].

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