Is closure recommended for patent foramen ovale and cryptogenic stroke?

**Patent Foramen Ovale in Cryptogenic Stroke**

**Not to Close**

Steven R. Messé, MD; Scott E. Kasner, MD

A quick PubMed search reveals an abundance of editorials, reviews, and opinion pieces on the subject of patent foramen ovale (PFO) management, and this is now the fourth published article on this topic that has adapted William Shakespeare’s classic words from *Hamlet* to describe the conundrum that faces neurologists, cardiologists, and their patients.1–3 The degree to which this title has been overused reflects the tremendous uncertainty that clinicians feel about patients who have had a stroke and are found to have a PFO. The reason for this confusion is that high-level, unbiased data do not yet exist to guide our clinical decisions with these challenging patients. The Food and Drug Administration rescinded the prior Humanitarian Device Exemption for percutaneous PFO closure devices to spur research into this clinical question.4 Unfortunately, although the National Inpatient Sample demonstrated a 50-fold increase in the number of percutaneous PFO/atrial septal defect closure procedures over a 6-year period ending in 2004, enrollment in clinical trials has continued to be slow, suggesting that many patients are receiving percutaneous PFO closure with the use of off-label atrial septal defect devices.5 The rampant off-label closure of PFOs is both hindering the progress of randomized controlled trials and undermining their validity. So, to answer the titular question: do NOT close the PFO, EXCEPT in the setting of a randomized trial.

Response by Windecker and Meier p 2004

**Background**

Leonardo Botallo, an Italian surgeon, is credited with the discovery of the foramen ovale in 1564.6 He noted a communication between the left and right atria in the fossa ovalis, formed by an overlap between the septum primum and secundum. In 1877, Julius Cohnheim, a German pathologist, described a case of a fatal cerebral embolism that he believed had passed through a PFO.7 Thus, he was the first to propose that a venous thromboembolism could bypass the lungs via a PFO and paradoxically enter the arterial circulation. The foramen ovale is an integral component of the fetal circulation, but it will permanently close in a majority of the population by adulthood. Autopsy studies have reported rates of PFO ranging from 17% to 27%.8,9 Estimates of PFO prevalence with the use of echocardiography have varied widely, but the largest population-based transesophageal echocardiography (TEE) study found a rate of 25.6%, comparable to the autopsy studies.10

An atrial septal aneurysm is defined by excessive movement of the interatrial septum throughout the cardiac cycle. Like PFO, multiple retrospective case-control studies have found an increased prevalence of atrial septal aneurysm in patients with cryptogenic stroke.11,12 However, the large

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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majority of atrial septal aneurysms are associated with a right-to-left shunt, and given the scope of this article, we will only discuss atrial septal aneurysm in terms of how it may modify the risk of recurrent stroke in patients with PFO.

PFO and Cryptogenic Stroke

It was not until the late 1980s that the first case-control study was published demonstrating an increased prevalence of PFO in patients with cryptogenic stroke, that is, stroke without an obvious etiology such as atrial fibrillation or carotid stenosis and not in a distribution consistent with small-vessel disease. This association suggested that PFO is a potential cause of stroke, and multiple subsequent case-control studies have similarly concluded that PFO is more prevalent among patients with cryptogenic stroke than among patients with known stroke etiology or subjects without stroke. Most of these studies have focused on younger patients because cryptogenic stroke is more common among the young, and an early study found that older stroke patients did not have a higher rate of PFO. Petty et al performed a retrospective case-control study that raised questions about the association of PFO and stroke by utilizing blinded interpretation of TEE to compare a population-based cohort with patients with stroke of known etiology and those with cryptogenic stroke and found no significant differences in PFO prevalence. The authors concluded that the association between PFO and cryptogenic stroke has been overstated because of selective referral of cryptogenic stroke cases and decreased detection of PFO in noncryptogenic stroke cases. A recent high-profile prospective case-control trial used TEE to evaluate >500 consecutive acute stroke patients and found that PFO was more prevalent in patients with cryptogenic stroke, both among younger patients (43.9% versus 14.3%; odds ratio, 4.70; 95% CI, 1.89 to 11.68; P<0.001) and, to a lesser extent, older patients (28.3% versus 11.9%; odds ratio, 2.92; 95% CI, 1.70 to 5.01; P<0.001). However, this study did not address the concerns raised by the article by Petty et al because patients were identified as cryptogenic or noncryptogenic before the TEE was obtained, and the interpretation of the echocardiogram was not done in a blinded fashion.

PFO and Stroke Risk

Limited data are available from 2 prospective population-based cohort studies suggesting that there is not a dramatically increased risk of first stroke among patients with PFO. Nevertheless, the primary clinical question facing neurologists and cardiologists is what to do when a PFO is identified after a patient has had a first cerebrovascular event. Many clinicians do not realize that studies have consistently found that the presence of a PFO does not inherently increase the risk of recurrent stroke. The best data addressing PFO and stroke recurrence come from 3 prospective cohort studies that have addressed this issue. Individually, none of these studies found an increased risk of recurrent stroke among cryptogenic stroke patients with a PFO compared with those without PFO, and a pooled analysis of the 3 studies found a relative risk of 0.95 (95% CI, 0.62 to 1.44). These studies evaluated patients across a wide range of ages. When the focus is on younger cryptogenic patients, the actual rate of stroke recurrence appears to be quite low, particularly compared with patients with known stroke mechanisms. For example, the French PFO/atrial septal aneurysm study enrolled patients with an average age of 42.5 years, and the average annual stroke and death rate was 1.5% for patients with a PFO who were treated with aspirin. In the PFO in Cryptogenic Stroke Study, patients younger than 55 years with a PFO had an annual risk of stroke or death of 1% compared with 4.7% for those patients without a PFO (hazard ratio=0.21; 95% CI, 0.02 to 1.78; P=0.15). Although the risk of recurrent stroke is ~1% for medically treated patients with PFO, patients with symptomatic large-vessel stenosis or atrial fibrillation face a risk of stroke recurrence that ranges from 6% to 20% per year. Thus, PFO does not confer an increased risk of stroke recurrence among patients with a primary cryptogenic stroke, and the actual stroke recurrence rate among younger patients is relatively quite low.

Some data may help to predict who may be at highest risk of stroke recurrence. The French PFO/atrial septal aneurysm study reported that patients with a PFO and concomitant atrial septal aneurysm had an increased risk of stroke recurrence. The average annual risk of stroke was 3.8% versus 1.8% for those patients with no atrial abnormalities (relative risk=2.98; 95% CI, 1.17 to 7.58). In contrast, among patients with any stroke subtype in the PFO in Cryptogenic Stroke Study, there was no association with increased risk of stroke recurrence among patients with both PFO and atrial septal aneurysm (8.0% versus 7.7%; relative risk=1.04; 95% CI, 0.51 to 2.12). Unfortunately, these data were not available for the cryptogenic stroke cohort alone. Although many retrospective case-control trials had determined that large PFOs had stronger associations with cryptogenic stroke, the prospective cohort studies did not confirm this finding. Furthermore, the validity of PFO size estimation via the most commonly used techniques—TEE and antecubital vein injection of agitated saline—is questionable at best. Other potential characteristics have been identified, including shunting at rest, Chiari’s network, and eustachian valve. However, their impact on stroke recurrence has not been validated conclusively.

Percutaneous PFO Closure

Retrospective comparisons and 2 small prospective nonrandomized cohorts suggested that PFO closure may be superior to medical therapy. Another small prospective cohort found no benefit of closure over medical therapy. A systematic review of nonrandomized studies of transcatheter closure (n=10) or medical therapy (n=6) for PFO reported a 1-year rate of recurrent neurological thromboembolism of 0% to 4.9% with transcatheter intervention and 3.8% to 12.0% with medical therapy. A more recent review of similar
retrospective or nonrandomized data reached similar conclusions. However, it is important to emphasize that there are numerous examples in the recent history of clinical medicine in which practice recommendations based on uncertain or low-level data have been found to be incorrect when less biased, larger studies are performed. Stroke prevention measures have been particularly prone to this error. For example, the use of hormone replacement therapy to reduce cardiovascular risk, warfarin for stroke prevention in symptomatic intracranial atherosclerotic disease, and bypass for carotid occlusion have all been shown to be lacking benefit or harmful in randomized controlled trials, in which they had been routinely prescribed previously on the basis of observational data. Thus far, there are no published randomized trials comparing PFO closure with medical therapy. Two trials are currently under way in the United States, including the Evaluation of the STARFlex Septal Closure System in Patients With a Stroke or TIA Due to the Possible Passage of a Clot of Unknown Origin Through a Patent Foramen Ovale (PFO) (CLOSURE 1) by NMT Medical Corporation and the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) by AGA Medical Corporation, and others are in various stages of development.

Despite the enthusiasm among invasive cardiologists to close PFOs, there are many potential reasons why percutaneous closure may not be effective. For example, obliteration of right-to-left-shunting often does not occur immediately after the procedure, and the PFO may, in fact, never close fully. Among 140 consecutive patients who received PFO closure, contrast-enhanced transcranial Doppler identified a residual large right-to-left shunt in 22% at 1 month and 9% at 1 year. Another series of 307 patients found a residual shunt in 15% of patients at 6-month follow-up. Finally, a series of 237 consecutive patients who underwent percutaneous PFO closure reported that at 360±267 days after PFO closure, transcranial Doppler with agitated saline contrast identified 20% with “incomplete closure” and another 14% with a “large” right-to-left shunt. Less than ideal results were also reported in another series of 110 consecutive closure patients with rates of complete occlusion of 51%, 66%, and 71% seen at 6 months, 1 year, and 2 years, respectively.

Both PFO and atrial septal aneurysm have been associated with atrial vulnerability to arrhythmia, including fibrillation. These findings present an alternative mechanism by which PFO may be associated with cryptogenic stroke. In addition, atrial arrhythmia after percutaneous PFO closure is not a rare complication. From a series of 456 patients who received PFO closure, the rate of episodes of new-onset, clinically detected atrial arrhythmia requiring therapy was 19% overall. Atrial fibrillation has been reported in up to 8% of patients in the immediate postprocedure period. Unfortunately, atrial tachycardias may not be restricted to the immediate periprocedural period. Among 71 patients who underwent PFO closure, 7% developed atrial fibrillation or flutter at an onset of 175±221 days. It is likely that these atrial tachyarrhythmias were related to the closure because they were significantly associated with use of a larger PFO closure device (P<0.05). Another study reported that patients who underwent PFO closure had a similar rate of atrial fibrillation detected by 7-day event loop recordings compared with other stroke patients with known stroke etiology, and the authors conclude that closure does not increase the risk of atrial fibrillation. However, the rate of atrial fibrillation was high in the PFO cohort (15%), and these patients were 16 years younger on average, with significantly less hypertension and diabetes and smaller left atrial size, smaller left ventricular mass, and less mitral regurgitation on echocardiogram compared with the patients with known stroke etiology. Each of these characteristics has been shown to predict atrial fibrillation, and thus it is surprising that they found as much atrial fibrillation in the PFO closure cohort as they did. In total, these studies raise the question of whether the PFO was truly the mechanism for the first event and whether PFO closure may, in fact, be trading one potential stroke mechanism (paradoxical embolization) for another (atrial arrhythmia) or, even worse, exacerbating the initial mechanism of stroke.

The effectiveness of PFO closure, if it exists, is undoubtedly also dependent on its safety profile. Numerous case series have concluded that percutaneous PFO closure is well tolerated, although the risk of complications is, in fact, not trivial. Serious adverse events have been reported to occur in ≈1% to 8% of patients. These risks include the aforementioned atrial fibrillation as well as retroperitoneal hemorrhage, air embolism, device embolization, cardiac puncture and tamponade, septal erosion, and clot formation on the closure device. In addition, a recent case series suggests that patients who undergo percutaneous PFO closure are at risk of the long-term development of new or worsened aortic regurgitation. Many of the publications describing outcomes from PFO closure are case series from single centers, and the patients were not routinely evaluated by a neurologist, suggesting that this may be a conservative estimate. For example, a case series of 35 patients who underwent percutaneous PFO closure received magnetic resonance imaging before and immediately after their procedure. Three (9%) were found to have acute infarcts on the follow-up magnetic resonance image, 2 of the patients were reportedly asymptomatic, and 1 of these patients complained of sensory changes. Importantly, the safety issues noted here are primarily derived from the same types of biased studies that address the efficacy of closure, and thus the risks of percutaneous PFO closure have not been elucidated completely. However, the recently published Migraine Intervention with STARFlex Technology (MIST) Trial, a prospective, multicenter, double-blind, sham-controlled trial to evaluate PFO closure for migraine prophylaxis, provides important insight into the safety of percutaneous closure. Among the 64 patients who received an implant, 7 serious adverse events were reported as possibly or
definitely related to the device, including 2 patients with atrial fibrillation, 1 with cardiac tamponade, 1 with pericardial effusion, 1 with retroperitoneal bleed, and 2 episodes of chest pain.

Finally, some cardiologists have suggested that percutaneous closure of a PFO may preclude long-term medical therapy and its attendant risks. After an ischemic cerebrovascular event, lifelong antithrombotic therapy is recommended for all patients. Furthermore, most patients are treated with dual antiplatelet therapy for some time after the PFO closure procedure (a regimen that has been demonstrated to increase the risk for fatal or major hemorrhage in stroke patients) and then given a single antiplatelet agent thereafter. There are no prospective data to support use of warfarin in patients with PFO, and thus antiplatelet agents are generally the preferred medical therapy. Therefore, there is no advantage of closure over medical therapy with respect to the risks of antithrombotic therapy.

**Conclusion**

It does not seem surprising that clinicians and patients are uncertain about what to do when a PFO is identified after a stroke, given the limited and, at times, conflicting data that exist. The bottom line is that the effectiveness and safety of percutaneous PFO closure are unknown at this time. We are not advocating that PFO closure be abandoned as a potential means to reduce secondary stroke risk in select patients. However, although there is a fairly well-established association between cryptogenic stroke and increased PFO prevalence, the risk of stroke recurrence is also established to be low, and the effectiveness and safety of percutaneous closure remain undetermined. This current situation will continue to foster unless clinicians get serious about encouraging patients to enroll in trials. It appears likely that study completion may require the cessation of off-label use of atrial septal defect closure devices. Perhaps the strongest motivation for clinicians is that if the patients most likely to benefit from PFO closure are closed outside of a randomized trial, the trials may fail to demonstrate a benefit. In that case, PFO closure will be deemed ineffective and possibly harmful with a high level of evidence, whether that conclusion is correct or not.

As stroke neurologists, we have often jealously marveled at the cardiologists’ ability to organize and efficiently execute randomized controlled therapeutic trials; thrombolysis for myocardial infarction has been studied in multiple trials involving >100,000 patients, whereas thrombolysis for stroke has been tested in trials involving only ~5000 patients. Yet for the case of stroke and PFO, the cardiologists who offer closure (and the insurers who pay for it) are actually impeding scientific progress by embracing an unproven therapy and thereby providing suboptimal care for their patients. It is time for the cardiology and neurology communities to stand up for scientific integrity in the face of uncertainty.

To borrow from the bard again, King Lear demanded, “I’ll see their trial first. Bring in the evidence.” Randomize!

**Disclosures**

Dr Messé has received research grants from NMT Medical and Gore for participation in ongoing trials of PFO closure. Dr Kasner has received research grants from NMT Medical and Gore for participation in ongoing trials of PFO closure.

**References**


Response to Messé and Kasner

Stephan Windecker, MD; Bernhard Meier, MD

An intellectual skirmish of cardiologists with neurologists in the leading cardiovascular journal should be a home run for the cardiologists. It is not. The neurologists Messé and Kasner eloquently float in a stream of misconceptions and misnomers. The prime misconception is to assess the risk of time bombs set to go off any time between now and ever by counting how many have detonated within a year or two. The fact that none exploded may simply mean that they were all set to blow up later. The prime misnomer is that a stroke in the presence of a patent foramen ovale (PFO) should be called cryptogenic. To blame documented atherosclerosis, atrial fibrillation, or prior myocardial infarction for a stroke is at least as speculative as to blame a PFO for it. The dogma that lack of proof of association is not proof of lack of association needs to be respected. Furthermore, among these stroke causes, PFO is easiest to eliminate. As for procedural outcomes and safety, PFO closure is a swift and safe procedure. Although technical success is virtually guaranteed, complete closure admittedly is not. In ≈5% of people, a significant shunt persists after a first attempt because of an incompletely covered rent or ≥2 separate holes. Significant complications were as high as 5% during device developments and during the operator learning curve. Recently, complication rates have been <1%. Although the intervention may induce atrial fibrillation, this adverse event is rare and usually transient, hardly carrying a risk for stroke. In contrast to the statement of our fellow neurologists, we submit that closure of a PFO after a PFO-attributed stroke obviates the need for chronic blood thinners and thereby avoids their small but significant risks of bleeding. From a scientific point of view, we agree that PFOs best be closed as part of randomized trials until the data are in. However, should the efficacy of PFO closure eventually be proven, we will be held accountable for hundreds of preventable strokes that occurred in control arm patients such as the patient mentioned by Messé and Kasner. He was randomized to medical therapy in a PFO/migraine trial and suffered a stroke shortly thereafter. We also will have to consider the countless strokes among patients with PFOs treated without closure outside of trials.
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