Is patent foramen ovale closure indicated for migraine?

**Patent Foramen Ovale Closure for Migraine**

Mark Reisman, MD; Cindy J. Fuller, PhD

Migraine is a heterogeneous primary headache disorder. Migraine prevalence in the general population of the United States is ≈28 million people (13%) and results in significant costs to the healthcare system. Aura consists of 1 or more focal neurological symptoms, such as visual, sensory, or speech disturbances, and is present in ≈30% of migraineurs. Cortical spreading depression (CSD), a neuroelectric phenomenon first described in the rabbit cortex and implicated in the genesis of aura, is characterized by a self-propagating wave of neuronal and glial depolarization followed by hyperpolarization across the cortex.

Patent foramen ovale (PFO) closure resulted in partial or complete relief of migraine symptoms in several retrospective, single-center studies. In these studies, PFO closure was performed for secondary stroke prevention or shunt-related conditions such as decompression illness in scuba divers. Because no diagnostic or provocative test exists to link PFO to migraine, it is difficult to discern which patients are most likely to respond to elimination of the right-to-left circulatory shunt associated with PFO closure. Migraineurs with aura have a higher prevalence of PFO than migraineurs without aura and nonmigraineurs and are ≈4.5 times more likely to have >50% reduction in migraine frequency after PFO closure than migraineurs without aura.

The goals of closing a PFO for migraine headache are to decrease headache burden and reduce functional disability (ie, inability to perform usual activities or go to work/school because of headache). Other possible clinical advantages of closure should not be overlooked and include reduction in paradoxical embolic sequelae such as ischemic stroke, myocardial infarction, and cognitive dysfunction. Although not previously reported, prevention of headache chronification by intervening with PFO closure in the more benign episodic time point of the disease may also be beneficial (Table 1). Current estimates are that 4% of the population experiences chronic migraine and in 75% it is a transformation from episodic migraine. Brain parenchymal changes have been seen with migraine, both in white and in gray matter. Eradicating the source of migraine may benefit these progressive pathological processes. This article will link together multiple aspects of migraine and PFO to make the

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**Table 1. Potential Benefits of PFO Closure in Migraine**

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Description</th>
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<tbody>
<tr>
<td>Reduction in headache frequency</td>
<td>Reduction in migraine-related functional disability with improved quality of life</td>
</tr>
<tr>
<td>Prevention of recurrent ischemic stroke/TIA</td>
<td>Prevention of other paradoxical embolic sequelae, eg, myocardial infarction</td>
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<tr>
<td>Prevention of decompression illness in divers</td>
<td>Prevention or reduction in progression of cognitive dysfunction</td>
</tr>
<tr>
<td>Prevention of migraine chronification and potential medication overuse</td>
<td>Prevention of brain parenchymal changes (white and gray matter)</td>
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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association. This article is Part I of a 2-part article. Part II appears on page 475.

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case that PFO closure, in the absence of an appropriately targeted randomized clinical trial, is warranted in a selected population of headache sufferers, and to introduce the term “PFO headache” into the lexicon of headache management.

**PFO and Migraine: Perspectives on a Link**

The prevalence of PFO in migraine with aura ranges between 41% and 89%, whereas it is between 7% and 34% in migraineurs without aura and between 20% and 25% in nonmigraine controls. This association is bidirectional in that the odds of a person with a PFO having migraine is 5.1 times (95% CI, 4.67 to 5.59) greater than that of a person without a PFO. Furthermore, mean size of right-to-left shunt as measured by transcranial Doppler (TCD) increases from controls without migraine, to migraineurs without aura, and to migraineurs with aura. Patients with both migraine and a history of stroke have the largest shunts.

The Migraine Intervention with Starflex Technology (MIST) trial detected a right-to-left shunt in 260 patients (60%) with migraine using transthoracic echocardiography of which 163 (38%) were interpreted as being due to a moderate or large PFO. In the remaining 97 patients with right-to-left shunt, 72 (16.7%) were small atrial or pulmonary shunts, 22 (5.1%) were large pulmonary shunts, and 3 (0.7%) were atrial septal defects. Several studies investigated the importance of PFO and atrial anatomy in migraine patients. One study demonstrated similar PFO diameter by balloon sizing and tunnel length in migraineurs and nonmigraineurs, but migraineurs conducted larger volumes of agitated saline to the cerebral circulation than nonmigraineurs at rest and following the Valsalva maneuver as measured by TCD. It is unclear why this would occur, but further investigation is warranted.

In another study, a prominent Eustachian valve and Chiari network were more frequently found in migraine with aura (100% of migraineurs with aura versus 55% of nonmigraineurs), which could explain increased right-to-left shunting. Another study focused on septal anatomy associated with migraine and found 13% of subjects with migraine had evidence of atrial septal aneurysm versus 1.9% of controls without migraine. The increased frequency of atrial septal aneurysm was predominantly driven by the patients with migraine with aura (28%) versus migraine without aura (3.6%).

The association between PFO and migraine headache has been established by studies reporting not only the elimination or reduction of migraine after closure of a PFO but also the triggering of headache in patients receiving devices for closure of atrial septal defects. Why the latter would occur is unknown but supports the provocative notion of a link between the heart and migraine and more specifically the atrial septum. Theories include platelet activation or thrombosis caused by the implant. One could speculate that the mechanism for headache in the nonimplant patient could be platelet activation within the tunnel, the overlap between the septum primum and secundum, of a PFO. This potentially turbulent segment between the 2 tissues could activate platelets, especially in the presence of an atrial septal aneurysm. Furthermore, our group recently studied a small sample of migraine patients and found that 24% (95% CI, 12% to 36%) were resistant to aspirin therapy, suggesting platelet hyper-reactivity. Clopidogrel and aspirin are more effective than aspirin alone in reducing headache exacerbated after PFO closure in the early follow-up period, indicating that platelet microaggregates may be responsible for postclosure migraine and may play a central role in the genesis of the headache.

A PFO with right-to-left shunt would require a susceptible neurological substrate and a vulnerability to a substance that bypasses the pulmonary circulation and induces headache. The endothelium of the pulmonary circulation has significant metabolic activity. The lung metabolizes, activates, or inactivates many compounds including vasoactive amines and other humoral substances. Prostaglandins E1, E2, and F2α are almost completely removed from the blood; serotonin is 85% to 95% removed; 70% of angiotensin I is converted to angiotensin II; and 80% of bradykinin is inactivated. Whether these unaltered substances increase the susceptibility of the brain to environmental or intrinsic migraine triggers is unknown at present.

**Genetics of Migraine and PFO**

Rare forms of migraine are inherited in a Mendelian pattern, and in these instances are caused by defects in ion channels or ion transport molecules. Unfortunately, the molecular pathogenesis of the more common episodic migraine remains unknown.

Atrial shunts may be inherited in an autosomal dominant fashion, which partially explains migraine inheritance in some families. Siblings of patients with stroke with PFO were more likely to have PFO than siblings of patients with stroke without PFO (odds ratio [OR], 3.64; 95% CI, 1.3 to 10.5; P=0.015), driven by the increased prevalence of PFO among female sibling pairs (OR, 9.8; 95% CI, 2 to 47.9; P<0.01). Persons with “shunt-associated migraine” are more likely to have a family history of migraine than those who had migraine without shunt, suggesting a genetic link. Atrial septal aneurysms are associated with migraine, indicating that these two conditions may be genetically linked in some individuals.

Methylenetetrahydrofolate reductase (MTHFR) polymorphism, specifically the common single nucleotide cytosine replacement by thymidine at base position 677, has been reported to increase the risk of migraine with aura in some case-control and cohort studies. The polymorphism is one of the most extensively investigated in cerebral ischemia and has been linked to stroke. In this regard, migraine could be considered an intermediate factor in the complex pathway from MTHFR<sup>C677T</sup> to ischemic stroke. Patients with migraine and aura who underwent PFO closure had a higher incidence of thrombophilia (P=0.007) and had significantly higher prevalence of hyperhomocysteinemia and MTHFR<sup>C677T</sup> mutation than nonmigraineurs who also under-
went PFO closure (31% versus 13%; \(P=0.038\)).32 Whether PFO connects the MTHFR polymorphism to clinical manifestations of migraine and stroke is provocative and warrants further investigation.

**Brain Parenchymal Changes in Migraine**

Some migraineurs have changes in the brain that can be detected by MRI. White matter abnormalities (WMA) are hyperintense signals seen on MRI characterized by gliosis, axonal loss, and ischemic demyelination resulting from microvascular damage. The pathogenesis of WMA includes acute ischemia due to disruption of blood flow in a perforating artery or chronic ischemia in the periventricular and deep white matter regions of the brain both of which are internal watershed regions with low perfusion. Confluent WMA are an important cause of cognitive decline and vascular dementia.33 WMA are seen more frequently in migraine with aura than in migraine without aura.14 Cerebral ischemia during attacks of migraine with aura might cause changes to the primary visual cortex, the area where aura arises.3 The OR of WMA in migraineurs was 3.9 (95% CI, 2.3 to 6.7) versus nonmigraineur controls in 1 meta-analysis.34 In the “Cerebral Abnormalities in Migraine Epidemiological Risk Analysis” study,14 migraineurs with aura had an increased risk of cerebellar WMA than did patients with migraine without aura (OR, 13.7; 95% CI, 1.7 to 112). The load of such hyperintensities is believed to be exponential to the duration and frequency of migraine attacks, suggesting that migraine is a progressive brain disorder. A recent study35 reported that women who had migraine with aura in midlife were more likely to have cerebellar infarct-type lesions when elderly (OR, 1.9; 95% CI, 1.4 to 2.6). The increased prevalence of cerebellar lesions was not seen in men with migraine with aura in midlife (OR, 1.0; 95% CI, 0.6 to 1.8).36 Patients with migraine and WMA who underwent PFO closure experienced significant improvement in migraine frequency, with a decrease from 32±9 to 7±7 in 6 months versus controls who did not undergo PFO closure (36±13 to 30±21 in 6 months).36 Migraine resolution was seen in 34% of the closure group and 7% of the controls \((P=0.007)\); in addition, only patients in the closure group reported a significant reduction in migraine severity.36

Gray matter changes have also been observed in migraineurs. Compared with matched nonmigraineur controls, migraineurs had areas of reduced gray matter density in the frontal and temporal lobes; however, migraineurs showed increased periaqueductal gray matter density.15 Migraine patients with aura had increased density of periaqueductal gray matter and the dorsolateral pons relative to migraine patients without aura.15 Repeated attacks of headache or aura have been shown to lead to iron accumulation in the periaqueductal gray matter, causing progressive impairment of the antinociceptive system that controls activity in the trigeminovascular system.37 The authors suggested that iron homeostasis in the gray matter was selectively, persistently, and progressively impaired in the migraine and chronic daily headache groups, possibly by repeated migraine attacks.

The potential for PFO closure to interrupt the development of gray and WMA that may contribute to cognitive dysfunction in migraineurs with aura33 should be studied as long-term end points in randomized PFO closure trials.

**Aura**

Approximately 30% percent of migraineurs have headaches preceded by 1 or more focal neurologic symptoms collectively known as aura.3 Aura symptoms, predominantly localized to the cerebral cortex, can include transient visual disturbances, marching unilateral paresthesias and numbness or weakness in an extremity or the face, language disturbances, and vertigo.1 The aura will often last for <1 hour. The proposed mechanism of aura is CSD, which is associated with transient decreases in cerebral blood flow that are most often posterior in origin, based on results of perfusion studies.3 These cerebral blood flow changes show an apparent anterior migration with time, and the magnitude of the decrement in cerebral blood flow seems to be smaller than that associated with ischemic injury.38

Approximately half of migraineurs with aura have PFO.4 It is theorized that the right-to-left shunt allows microemboli and vasoactive substances to escape pulmonary filtration and be conducted to the cerebral circulation, where they can produce transient ischemia and CSD.6 Aura is initiated in the occipital lobe, supplied by the posterior circulation.3 TCD studies have detected a significant propensity for paradoxical emboli in the posterior circulation in patients with right-to-left shunt,39 which may be due to altered vasomotor reactivity in this region. The occipital lobe has been identified as a predominant area of infarct in patients with migraine and aura.40 However, microemboli from PFO or other right-to-left shunt may trigger aura by producing transient ischemia, leading to CSD. In support of this hypothesis, injection of polystyrene microspheres into the carotid artery of anesthetized mice triggered CSD without MRI evidence of cerebral infarctions.41

Not all migraineurs with aura have typical aura symptoms, and aura symptoms can occur without subsequent headache.1 Atypical aura and aura without headache may be subject to misinterpretation as transient ischemic attacks (TIA). The inconsistent relationship between aura and pain lateralization, the occurrence of aura with other primary headaches, and the observation that some treatments improve aura but not pain further confound the diagnosis. The prevalence of PFO is reportedly different between migraineurs with typical and atypical aura (46.3% and 79.2%, respectively; \(P=0.009\)).42 Typical aura without headache affects ≈4% of migraine patients,3 although it is unknown how many of these patients have a PFO. This condition is characterized by paroxysmal episodes of prolonged visual auras; atypical sensory, motor, or visual aura; confusion; dysarthria; focal neurological deficits; or gastrointestinal manifestations or other constitutional symptoms with or without a headache.1 The high degree of overlap in...
visual, motor, speech, and sensory symptoms between aura and TIA may become key features in the ability to identify patients who could benefit from PFO closure.

Migraine and Stroke: The PFO Bridge
The association between migraine and stroke is well recognized. Despite the many hypotheses linking the 2 disorders, the precise mechanism is unknown. Migraine and stroke may share common processes in the central nervous system. Both are characterized by release of inflammatory mediators and increased platelet reactivity and share common processes in the central nervous system. Both migraine and stroke may be due to patient selection. Table 2 outlines differences between MIST and nonrandomized studies in eligibility criteria and methodology. Two randomized double-blind studies, ESCAPE and MIST II, investigating PFO closure for migraine were recently discontinued in the United States. Both trials were plagued by slow enrollment predominantly due to narrow inclusion criteria. At our MIST II site, many of our patients that were screened exceeded the upper limit in headache days, and thus were excluded.

Future Trial Design
The challenges of MIST, MIST II, and ESCAPE offer direction for future randomized trials to gain acceptance for PFO closure for migraine prevention. The results of the MIST trial should be carefully analyzed, so that future investigators can be better directed to trial design and patient selection. It is critical to enroll patients who have similar characteristics that can be better directed to trial design and patent selection. It is

PFO Closure and Migraine
Observational Studies
Since the initial report that prophylactic closure of a PFO in divers led to an amelioration of migraine and the high incidence of PFO in migraine patients, there have been >10 observational studies that have reported reductions in migraine frequency after PFO closure for reduction of recurrent stroke or TIA risk. On average, PFO closure brought about complete resolution of migraine attacks in 57% (range, 29% to 84%) and an improvement in 43% of patients (range, 8% to 83%). A study by our group demonstrated headache relief in patients who had residual shunt after PFO closure but a significant reduction in conduction of microbubble contrast as determined by TCD. Larger shunts are more likely to be associated with migraine with aura versus smaller shunts. These results support the hypothesis of a “neurological threshold” of the brain to noxious substances, and that partial or complete PFO closure may reduce conductance of these substances below the level that triggers migraine.

When discussing migraine in nonrandomized open-label studies, it is impossible to avoid implicating the placebo effect, especially when patients are improving in the presence of residual shunts. In an analysis of migraine prevention studies, the placebo effect is 14% to 50%. Interestingly, the placebo effect is stronger in the setting of double-blind studies, and the placebo response is less in patients with more significant symptoms. However, in early PFO closure studies, preprocedural expectation of headache relief was absent.

Randomized Trials
To date the only large randomized trial to be completed for PFO closure in migraine was the MIST trial, a courageous attempt to validate in a double-blind, prospective, randomized trial results seen in retrospective single-center studies of cessation and reduction in migraine headache. The failure to meet both the primary (cessation of headache) and the secondary (>50% reduction in headache frequency and days) end points were a disappointment to many clinical researchers, who had observed patients with remarkable improvements in headache and function after PFO closure. So what happened? Much has been written about the overreaching primary end point, the substandard operation, and adjudication of the trial results. The failure of the trial may primarily be due to patient selection. Table 2 outlines differences between MIST and nonrandomized studies in eligibility criteria and methodology. Two randomized double-blind studies, ESCAPE and MIST II, investigating PFO closure for migraine were recently discontinued in the United States. Both trials were plagued by slow enrollment predominantly due to narrow inclusion criteria. At our MIST II site, many of our patients that were screened exceeded the upper limit in headache days, and thus were excluded.
headache frequency alone. Migraine researchers have expanded beyond “motor tract” symptoms and are now adjudicating with greater focus the effect on cognitive function. We have recently completed the Retro study (Reisman et al., unpublished data), which included patients with PFO and documented migraines who underwent PFO closure. The patients were interviewed systematically by an independent migraine expert to better distill from the patients a consistent symptom constellation that identifies those who may achieve the greatest benefit from PFO closure. The presence of prolonged aura, focal neurological deficits, and exertional headache were prominent in these patients. In a systematic analysis,9 criteria used for PFO closure in migraineurs included all of the following: shunt present during normal respiration; curtain shunt pattern on TCD; presence of atrial septal aneurysm; class 3 to 4 Migraine Disability Assessment score, indicative of moderate to severe functional disability; symptomatic significant aura; coagulation abnormalities (eg, Factor V Leiden, MTHFRC677T mutation, protein C or protein S deficiency, anticardiolipin or antiphospholipid antibodies, and antithrombin III); and migraine refractory to conventional drugs

Migraine frequency
No stringent criteria5,8 frequently episodic migraine headaches
Migraine with symptomatic, significant (prolonged) aura
Migraineurs5,8
Migraine with class 3 or 4 Migraine Disability Assessment score
At least 5 migraine days per month, but at least 7 headache-free days per month
Atrial anatomy
Included19
Atrial septal aneurysm or other persistent embryologic structures such as Eustachian valve, Chiari network
Large right-to-left shunt following Valsalva maneuver
Medication failures
Not applicable or not reported6
History of stroke and TIA
Included4,8
Coagulopathies
Included6
Coagulopathies included all of the following: shunt present during normal respiration; curtain shunt pattern on TCD; presence of atrial septal aneurysm; class 3 to 4 Migraine Disability Assessment score, indicative of moderate to severe functional disability; symptomatic significant aura; coagulation abnormalities (eg, MTHFRC677T); and migraine refractory to conventional drugs (Table 3). After a follow-up of 10±3.1 month (range, 6 to 14), patients who met these inclusion criteria had statistically and clinically significant improvements in migraine symptoms (mean change in Migraine Disability Assessment score 3.0±2.1, P<0.03).9

On the basis of these previous studies, we can begin to define the characteristics of the PFO headache (Table 3). Future randomized PFO closure trials should be designed to target migraine patients who will derive the most benefit from PFO closure, based on these inclusion criteria.

### Conclusion

Migraine is not only a painful headache but also a functional disability that robs individuals of their ability to work and have normal family and community interactions. In a recent survey, 44% of American Headache Society members supported use of an invasive procedure (either PFO closure or neurostimulator) for treatment of intractable headache.50 This is a testimonial to the need for additional and more effective treatments for migraine. PFO closure has the potential not only to reduce the functional disability of migraine but also to reduce the risk of stroke in young, otherwise healthy individuals. In addition, it may have a disease-modifying effect on brain parenchyma to reduce cognitive dysfunction. The impressive results seen in single-center, nonrandomized studies cannot be ignored. Challenges to adoption of PFO closure as a treatment for migraine include completion of randomized trials that have appropriate inclusion criteria, realistic end points, adequate statistical power to detect differences between closure and placebo groups, and sufficient duration of follow-up. The ability to establish a unique fingerprint for the PFO headache that distinguishes it from the spectrum of migraine headache is critical in the evolution of this therapy. Whether this fingerprint is based on symptoms, atrial anatomy, degree of shunting, genetic factors, a provocative test, or a combination of criteria will become clearer with further research.

### Disclosures

Dr Reisman received a grant from Coherex and has served on the scientific advisory board for Coaptus Medical. Dr Fuller received a grant from Coherex.

### References


Response to Reisman and Fuller

John D. Carroll, MD; Eugenia P. Carroll, MD

Drs Reisman and Fuller have written an exciting review and outline the many tantalizing links, suggesting a causative relationship rather than a statistical association, in some patients with both patent foramen ovale (PFO) and migraine. They propose the term “PFO headache” as part of a plausible hypothesis built on their review of the literature and extensive clinical experience. Table 3 in their article is useful as a preliminary step toward identifying hints and potential “clinical pearls” that a patient may have PFO headaches. The potential tautology is that a PFO headache will disappear with closure of the PFO, whereas the persistence of migraine post–PFO closure indicates it was not a PFO headache. In the absence of definite clinical characteristics as an accurate and validated means to identify patients who would benefit from having their PFO closed, there will be the need for a novel provocative test. Drs Reisman and Fuller state “a PFO with right-to-left shunt would require, a susceptible neurological substrate and a vulnerability to a substance that remains noxious to the brain when bypassing the pulmonary circulation to induce headache.” Rarely, migraine is precipitated by the venous injection of the standard agitated saline-blood bolus to detect shunting. Perhaps, an additive is needed to mimic the natural onset of a migraine, a PFO-headache producing cocktail, so to speak, to enhance the diagnostic yield. The safety and reversibility of such a central nervous system stress test would need to be assured. We are in agreement that further research, not off-label, noninvestigative PFO closure, is needed to investigate the potential role of PFO closure in some subsegment of the large population of migraineurs. Research is needed to prove true causation of PFO and shunting in migraine pathophysiology. It is an unacceptable approach of simply implanting a permanent device in thousands of individuals suffering from migraine and then retrospectively trying to figure out why some had a therapeutic effect. The question remains how such a series of studies can be organized, designed, and funded.
Is patent foramen ovale closure indicated for migraine?

**PFO Closure Is Not Indicated for Migraine**

“Don’t Shoot First, Ask Questions Later”

John D. Carroll, MD; Eugenia P. Carroll, MD

The experimental field of patent foramen ovale (PFO) closure for migraines is in an unsettled state and, in some ways, a damaged field of investigation, due to the failure of 1 randomized trial to show benefit and others that were aborted. The closure of a PFO in a patient with migraine as the indication remains a highly experimental act that absolutely should be done only in the context of institutional review board approved research with a well-informed patient in a clinical trial that is designed and managed with leadership from neurologists who are expert in migraine. Interventional cardiologists should “back off” and serve as consultants for clinical trials as experts in the procedure, not the disease, and not the management of the disease. In clinical practice, PFO closure for migraine is absolutely not indicated. In clinical research, there remain major unanswered questions in the pathophysiology of migraine, and the identification of any migraine subsets that may have an acceptable response rate to PFO closure.

**Response by Reisman and Fuller on p 481**

**Level of Evidence and Quality of Data Are Problematic**

As of January 2009, there are 9 retrospective trials, 4 prospective trials, and 1 randomized trial in the area of PFO closure and migraine that were reviewed.1–14 Table 1 presents many of the limitations and flaws in these trials if the reader looks past the generally positive results in the headlines. Applying the standards used in clinical guideline development used by the American Heart Association/American College of Cardiology, the body of evidence would be dismissed as incomplete, contradictory, and not ready for even mention in clinical guidelines.15

Retrospective and prospective trials may lead to much enthusiasm for a treatment but the history of interventional cardiology, and other areas of medicine, is full of examples of treatments failing when subjected to the rigors of randomized trials. Such is the case of the PFO closure-migraine field as of today.

The Migraine Intervention with STARFlex Technology (MIST) trial published in 2008 was a sham-controlled, blinded trial.14 The trial was clearly a negative trial and remains the 1 completed and published randomized trial in PFO closure for migraine that has dashed hopes for more clarity in the field, let alone a step toward device approval for this indication. As outlined in Table 2 and fully discussed in a previously published editorial, the MIST trial was seriously flawed and had uncovered many of its own limitations, despite its bold design and timing early in the PFO closure experience.16

The results of the MIST trial cannot be ignored and are not easily discounted, despite the study’s shortcomings. It...
CLOSURE.18 In October 2008, a second device company to focus its financial resources on their PFO/stroke trial, MIST II, on January 23, 2008, migraine. NMT Medical, Inc (Boston, Mass) closed its light of understanding the role of this potential treatment for 2008 does not bode well for moving out of the dark into the silence.

"The collapse of 2 randomized trials in the United States in 2008 does not bode well for moving out of the dark into the light of understanding the role of this potential treatment for migraine. NMT Medical, Inc (Boston, Mass) closed its US-based PFO/migraine trial, MIST II, on January 23, 2008, to focus its financial resources on their PFO/stroke trial, CLOSURE.18 In October 2008, a second device company decided not to finish a randomized, sham-controlled migraine PFO closure trial, the ESCAPE trial from St Jude Medical Corporation, with the full name of “On Effect of Septal Closure of Atrial PFO on Events of Migraine With Premere.”19,20 The sponsoring company of the ESCAPE trial decided to abort the study after only 56 patients of a planned 492 subjects had been enrolled in a period of 2 years. It is unclear whether and when any meaningful data from these 2 trials will see the light of day. Two additional randomized multicenter studies sponsored by AGA Medical Corporation remain active. Percutaneous closure of PFO in migraine with aura started in Canada and Europe and the Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the Amplatzer PFO Occluder Compared With Medical Management (PREMIUM) started in the United States in July 2006 with ~400 patients to be enrolled.21

**The Broader View and the Quagmire of PFO Closure in 2009**

PFO closure for a variety of conditions is being studied but has not yet had the benefit of 1 randomized trial being

is hard to be definitive about its impact, but it has played a major role in the general loss of confidence in the likelihood of proving the primary hypothesis, the ability to enroll patients in new trials, and whether the field will move forward relying only on industry-sponsored device trials in such a complex disease.

In our own involvement in one of the randomized trials, the very different anecdotal responses to PFO closure have been striking. One patient was totally freed from the migraine-induced misery. Another saw absolutely no difference having her PFO closed. A third woman could not discontinue clopidogrel because of the onset of incessant aura. Seeing through a glass, darkly, does describe the state of PFO closure studies.

### Table 1. Frequent Weaknesses and Limitations of PFO Closure for Migraine Trials

| Design | Mostly retrospective,1–9 a few prospective,10–13 only 1 randomized trial14
| Patient population | Mixed patient populations included often with CVA/TIA1–12
| Methodology | Self-reporting of end point of trial by patients, often retrospectively, with known high-placebo response rates1–14
| End points | Lack of standardization of prespecified end points often with multiple variations1–9
| Results | PFO anatomy and physiology incompletely characterized1–14
| | Wide variation in procedure complications rates and completeness of reporting
| | Limited duration of follow-up in a chronic disease with major activity fluctuations1–11,13,14

**Table 2. Issues With MIST**

| Positives | Landmark trial with randomized sham-control group investigating novel heart-brain interaction
| | Discovered important issues in trial design
| | Raises the issue of the medical refractory migraine population may be the least responsive to PFO closure
| | Reaffirmed the high frequency, 60%, of right to left shunting in this migraine population

| Negatives | Relatively small number of patients
| | Unreasonable primary end point of absence of all migraines after closure
| | Lack of independent echocardiography core laboratory and standardized echocardiographic techniques resulting in debatable residual shunt rates
| | Methods and published results did not allow clear identification of pulmonary shunts and residual intracardiac shunts confounding the clinical outcomes
| | Device used might have had high residual shunt rates
| | High rate of procedure-related complications
| | PFO closure performed with insufficient experience and early in the learning curve of PFO implantation technique development
| | Inclusion of chronic daily headache patients
| | Studied a group of migraineurs who were quite refractory
| | Migraine data gathered early after closure when closure may be incomplete in some
| | Initial presentation of positive secondary end point which became negative in final publication and disagreements between sponsors and some investigators clouded the credibility of the published results and prevented further analysis
| | Negative results without the ability to understand the reason(s) has lead to challenges in how research and future trials should be modified

**Discovered important issues in trial design**

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**Negative results without the ability to understand the reason(s) has lead to challenges in how research and future trials should be modified**
completed that proves its value over another therapy. The state of equipoise exists in the area of PFO closure for cryptogenic stroke versus medical therapy, but for PFO closure for migraine, we argue it has not even reached the stage of being on the same scale as medical therapy for migraine. Pioneers in migraine medicine consider the PFO closure field an enigma.

Premature legitimatization of off-label PFO closure in clinical practice will lead to a repeat of the mishandled emergence of PFO closure for prevention of recurrent cryptogenic stroke. All efforts must be put forward to maintaining the investigative nature of the procedure until an unequivocal clinical trial base establishes the benefits, the risks, and the appropriateness of the procedure in the diverse population of migraineurs.

The argument against PFO closure for migraines needs to extend to a broader consideration of issues other than the clinical trials published to date. These include problems intrinsic to industry-sponsored trials, the process of Food and Drug Administration regulation of the device approval process, and the minimally regulated process of dissemination of new interventional procedures in the United States.

The benefits of a robust and innovative device industry in providing new technology to improve the care of our patients are enormous. They are the sole source of bringing these advances to the bedside. Industry sponsorship of clinical trials in new cardiovascular devices has been critical because few alternatives are available. But occasionally, as demonstrated in the MIST trial, there is a lack of data transparency, and the resultant conflict between investigator and sponsor disrupts the scientific process and highlights the tension between commercial interests and scientific goals. Confidentiality of intellectual property is a legitimate concern of sponsors. On the other hand, standards exist that should guide investigators’ participation in the study design, access to data, and control over publication.

The failure of 2 randomized, sham-controlled trials of PFO closure in migraine to be completed needs to be analyzed and acted on. There is appropriate sadness and anger in one’s initial reaction to the prematurely closing of these 2 studies for the hundreds of courageous patients who agreed to participate and often donated their time to the clinical trial process that is critically important to advances in medicine.

Through negotiations among the sponsor, the Food and Drug Administration, and physician investigators, a trial design is agreed to and approved. Poor enrollment was at the heart of the 2 aborted migraine trials, and the reasons need to be understood. Until proven otherwise, the responsibility for these failed trials must be shared by all parties and not perfunctorily ascribed to financial decisions by a sponsor. Excessively restrictive inclusion/exclusion criteria, excessive burden of documentation, and other factors leading to a study that is too expensive to complete and doomed to fail must be examined. As discussed in an editorial in the journal of the American Headache Society, Headache, MIST II had Food and Drug Administration mandated requirements that made the study execution and enrollment excessively daunting for investigators, the company, and patients. With 30,000 hits to the study website, 1400 patients screened, 376 referred to MIST II centers, it is quite sad to hear that only a “very, very few were actually randomized.”

As previously discussed, a migraine indication for PFO closure will only be won if both benefit and reasonable risk are proven. There is no reason to believe that PFO closure complication rates will escape some relationship to institutional and operator volume. The very low complication rates of large experienced centers such as Bern, Switzerland as opposed to the high and perhaps early learning curve related rates in MIST as should drive us to consider in the United States promoting the “centers of excellence” concept. Our European and Canadian colleagues have systems in place that do centralize highly specialized care, whereas the United States system has minimal restraints preventing virtually all hospitals from being able to start programs in PFO closure and other specialized interventions in structural heart disease. These training and experience-related quality of care issues are important if PFO closure in migraine eventually attains approval by the Food and Drug Administration.

The Pathway Out of the Quagmire
Completion of the 1 remaining US-based trial and 1 European-Canadian trial is a major next step and top priority. Let us hope that those who advocate PFO closure as an established indication for migraine do not undermine completion of these trials. Let us hope that the trials have not been so overregulated that they are aborted.

Neurology needs to provide primary leadership in this field. Most of the published reports of PFO closure and migraine have been in cardiology journals rather than neurology journals. But it is the general practitioner and neurology community who manage these patients and indeed it is clear that many patients with more severe migraines end up seeing headache specialists. Headache clinics and migraine hospital services are critical for the performance of clinical trials of PFO closure in migraine. The negativity and controversy of MIST and the 2 aborted US trials have potentially strained their willingness to participate in future trials. The Editor-in-Chief of Headache, the official journal of the American Headache Society, further articulates the headache specialist’s current view of PFO closure-migraine trials: “until these or other studies can demonstrate clear evidence of safety and benefit associated with PFO closure for migraine, that procedure cannot be considered a viable part of the therapeutic arsenal used for migraine prevention.”

Leaders in the academic neurology field go further to question the causal link between PFO and migraine with aura. They review the insufficient evidence, the contradictory data, and emphasize that “migraine is a complex and heterogeneous disorder that is influenced by a number of genetic and environmental factors, and responder rates to available preventive medication are only ≈50%.” Even the...
neurologists who have published in the PFO-migraine arena have recognized the early stage of the research. For example, a leading investigator in Europe writes in January of 2009, “For the time being—pending the results of the ongoing trials—although the association between PFO and migraine with aura seems established, it seems premature to recommend PFO closure for migraine on a general basis.”32 Another world leader in migraine goes on the record in January 2009 that “the association between migraine and PFO remains an interesting area for investigation.”33 In his article on the emerging therapies for migraine, PFO closure is given a small and generally negative place in his article. PFO closure is not mentioned in his conclusions and neurostimulation is proposed as the most promising device-based strategy. We could find no leading migraine expert who has written in support of the protagonist viewpoint that PFO closure is currently indicated for migraine.

Clinical trial design and execution in the study of migraine have been formally addressed by the task forces of the International Headache Society.34,35 These guidelines were developed for drug trials and not device trials. For PFO closure and nerve stimulation trials, it is important that these guidelines be modified. This will not only provide the needed leadership and expertise from the neurology-migraine community but also will help address the many flaws and variability in the PFO-closure trials for migraine listed in Table 1.

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A major improvement in clinical trials design is to incorporate the accepted classification of the 6 major subtypes of migraines and use the HIS scheme.36–38 As summarized in Table 3, there is a somewhat complex classification system and clearly goes beyond the simplistic notion that asking the patient if they have migraines is adequate for a cardiologist to consider inserting a PFO device. The need to incorporate an accepted classification scheme takes on new meaning because recent data were presented in late 2008 on the high frequency of right-to-left shunting in the chronic migraine group versus a control group. These patients are quite different from the episodic migraineurs who have previously been studied,39 but there are no data to believe they will respond to PFO closure.

The concept of a “responsive subgroup of migraineurs to PFO closure” has emerged, but it remains a hypothesis waiting to be tested. The group of patients with migraines and a cryptogenic stroke represent an overlap of the clinical syndromes associated with significant right to left shunting through a PFO (Figure 1) and seem to favorably respond to PFO closure, although these studies are flawed (Table 1). The trials showing reduction in migraine relief after PFO closure for stroke did not consider the natural evolution of migraine after a stroke.40

Recently, migraineurs who have subclinical MRI lesions have been studied before and after PFO closure.13 This open observational study brings MRI into a PFO closure study but has serious shortcomings.33 Others have presented data that these MRI lesions are as common in those without a PFO as those with a PFO.41

Pathophysiology Research Is Needed, Not Only Device Studies

Not only are new trial designs needed but also a commitment to understanding the PFO-migraine connection and sorting out whether it is more than an association (Table 4). The pathophysiology of PFO-enabled stroke through the mechanism of paradoxical embolism has a much more solid base. It has been directly observed plus alternative causes for stroke have been sought and found to be not present. The patho-
shunting of microemboli through a PFO. In the presence of serotonin-rich platelets, on a newly implanted device, response and presumably works through reduced aggregation of platelets.

The use of clopidogrel effectively blocks this process and may have been a factor in the MIST trial. Device thrombosis is indeed a rare event but may be associated with a high rate of symptoms. It has been observed that new onset migraine or worsening of pre-existing migraine can occur in some patients after device closure of PFO and atrial septal defect. The use of clopidogrel effectively blocks this response and presumably works through reduced aggregation of serotonin-rich platelets, on a newly implanted device.

Another potential trigger for migraines may be right-to-left shunting of microemboli through a PFO. In the presence of an underlying cortical hyperexcitability, showers of microemboli may trigger the onset of migraine and the subsequent cortical spreading depression associated with aura.

Table 4. Recommendations to Exit From the Quagmire of PFO Closure and Migraine

| Neurology leadership and ownership in trial design, conduct, and in the promotion and completion of these trials |
| Research on migraine pathophysiology and identification of patients who will and will not respond to PFO closure |
| Replace industry sole sponsorship to joint sponsorship with scientific groups such as the National Institutes of Health |
| Combine pathophysiology research with device trials |
| Food and Drug Administration reform that promotes completion of important clinical trials in a fashion that is timely and cost-conscious |
| Promote and institute centers of excellence in structural heart disease interventions to augment quality but also collect, analyze, and publish critically needed data in clinical trials |
| Inclusion of patient advocacy in clinical trials |

Serotonin is a candidate “bad humor” based on several lines of evidence. It has been shown that a significant increase in plasma serotonin and urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) can be detected during migraine. This has provided a biochemical justification for tryptan therapy for migraine. It has been observed that new onset migraine or worsening of pre-existing migraine can occur in some patients after device closure of PFO and atrial septal defect. The use of clopidogrel effectively blocks this response and presumably works through reduced aggregation of serotonin-rich platelets, on a newly implanted device.

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Figure 2. X-plane display of a transesophageal echocardiogram showing a large mobile thrombus (dimensions in green) on the right atrial surface of a double umbrella device (arrows) used to close a PFO. Infranet but serious complications of the implantation procedure and related to the device itself are important in the final assessment of the risk/benefit ratio of PFO closure for migraine. It remains to be demonstrated if new approaches to PFO closure will be shown to have less risk.

Approaches to PFO Closure

The closure procedure and operator errors are only one of the sources of complications from PFO closure that will impact on the acceptance of this therapy for migraines. If a device fails to substantially close the PFO then persistence of symptoms would be expected and may have been a factor in the MIST trial. Device thrombosis is indeed a rare event but may be associated with a high rate of symptoms. It has been observed that new onset migraine or worsening of pre-existing migraine can occur in some patients after device closure of PFO and atrial septal defect. The use of clopidogrel effectively blocks this response and presumably works through reduced aggregation of serotonin-rich platelets, on a newly implanted device.

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Calling for research on pathophysiology may seem naive, given the dominance of industry sponsorship of research that is focused on the device approval process. On the other hand, it is a fundamental truth that migraine often occurs without a PFO, that PFOs are incidental in many migraineurs, and that PFO closure is not expected to work in many migraineurs. The identification of subgroups that are potential targets for a successful clinical trial will not occur until more is understood. MRI studies, searching for objective serum or imaging markers for migraine, genetic studies, and trying to understand the environmental aspects of the disease may, in fact, be in the interest of device companies. Another approach would be to have a scientific arm supported by the National Institutes of Health that would run in conjunction with a device trial in PFO closure for migraine.

Without a scientific basis and understanding of pathophysiology, this field may be destined to fail because the true responders will have their improvement overwhelmed by nonresponders to PFO closure that will dilute the therapeutic effect in these relatively small studies. Our line of reasoning is that PFO is currently not indicated for migraine because we have failed to show in a randomized blinded trial that migraineurs benefit from PFO closure, we have not even identified why migraineurs should respond, and we have failed to identify which patients will respond so as to avoid the placement of many devices that will do nothing beneficial for many patients.
matched to anatomic variations but do not address the fundamental unanswered questions of the role of PFO closure in migraine and the risk/benefit balance that is acceptable to patients and others involved in the decision making.

Final Thoughts for the Patient

On a clinical practice level, it is important for patients to realize that it is now impossible to predict whether they would respond to PFO closure. The better chance is that they will not and that the pilot studies to date have studied only a very small fraction of the diverse spectrum of migraine patients. Their desperation in finding some relief from their suffering is inappropriately and unwisely directed to push for closure using off-label devices in 2009. Only in the 2 remaining randomized trial should they seek this experimental approach. Patients with migraines are encouraged to push for reform including better designed trials that are completed in a timely fashion and provide definitive answers. As things stand today, this very common problem and this potentially exciting treatment are not being well studied, and the field is driven by the device industry and their varying ability to fund studies to completion in the current regulatory environment. Migraineurs should first and foremost be dismayed and angry with the failed clinical studies and our inability to answer the question, "Is PFO closure indicated for migraine?" Other exciting developments in the genetics of migraine and other migraine therapies are progressing 33–42. PFO closure for migraine is currently an innovative and promising treatment but one that we should not apply the gunslinger approach of "shoot first, ask questions later."

Disclosures

Dr. J. Carroll is a consultant for AGA Medical, Coherex, Coaptus, Gore, and Philips Healthcare. He has research contracts and receives speaking honoraria from AGA Medical and Philips Healthcare.

References

Response to Carroll and Carroll

Mark Reisman, MD; Cindy J. Fuller, PhD

The article by Carroll and Carroll, provocatively titled “Don’t Shoot First, Ask Questions Later,” implies that the authors believe that current evidence for patent foramen ovale (PFO) closure in migraineurs has insufficient scientific rigor to recommend this therapy. Another potential title could have been “Aim Before You Shoot.” Migraineurs are a heterogeneous population, and failure to discern a priori those who are most likely to benefit will continue to undermine PFO closure as a therapy. In the United States, much of the research support comes from medical device companies attempting to gain approval for PFO closure devices to treat the large migraine population. The onus for demonstrating a connection between PFO and migraine should not be on industry. Their responsibility should be to provide the devices to treat patients and demonstrate safety and efficacy. A search of 2009 funding on the National Institutes of Health Web site showed 5 new migraine R01 or R21 awards, none pertaining to PFO. This emphasizes the need for more neurologists and cardiologists to collaborate in investigating the mechanism of the PFO headache. The article by Carroll and Carroll is not antagonistic to our position but represents a natural progression of challenging a new and novel hypothesis of linking migraine and right-to-left shunts. PFO migraine research has been out of sequence, with clinical trials preceding the definition of a clear targeted headache population. However, we should neither neglect nor negate the evidence accumulated to date, and we should continue our commitment to addressing these less-than-optimally-cared-for patients.
Is patent foramen ovale closure indicated for migraine?: PFO Closure Is Not Indicated for Migraine: "Don't Shoot First, Ask Questions Later"
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