It might seem more like a condition for the cardiologist than the neurologist, but over the years the neurology community has been paying more attention to patent foramen ovale. A number of recent studies have added to the mounting evidence that a hole in the heart may have a direct influence in matters of the brain, as it can play a role in stroke and migraine. However, some of the most recent data have presented paradoxes that raise questions about how to handle PFO patients.

If there is an underlying connection, it is certainly worth finding. According to existing estimates there are approximately 40 million people with PFO in the United States. Many of these patients will likely live their whole lives unaffected by the condition and never even know they have it. But those who suffer from a cryptogenic stroke or migraine typically need some form of treatment, and if closure has the potential to help, it could prove invaluable.

In this article, we’ll look at what the existing research indicates about the complex relationships among stroke, migraine and PFO. We’ll also consider what the possible interrelation between these conditions means in a clinical setting.
Hole in the Heart, Pain in the Head
Many headache and pain management experts have been following the connection between migraine and PFO, as recent data seem to indicate an empirical connection between these two conditions. Migraine with aura appears more often in patients with PFO than in the general population, although the reason remains elusive. There are some data indicating that closure can lead to a reduction in migraine frequency, and even some anecdotes of closure leading to complete elimination of migraine.

A poster presented at the 2006 International Stroke Conference in Kissimmee, FL this past February indicates there may be some value in looking further at whether or not closure can improve migraine symptoms. David E. Thaler, MD, PhD, Assistant Professor of Neurology and Director of the Comprehensive Stroke Center at Tufts-New England Medical Center in Boston, examined a database of transeosophageal echocardiograms performed at a single center over one year. The patients were classified into three groups: 40 with PFO who were about to undergo closure, 63 with PFO who were treated medically, and 63 age- and sex-matched controls.

In accord with prior research, Thaler's group found migraines were more common in the PFO patients than controls in 58 percent of the group planning PFO closure, 41 percent of the group with PFO on medical therapy, and 16 percent of the control patients. Over a one-year period after PFO closure, 13 patients (33 percent) in the closed group reported reduced migraine severity, with one reporting more severe symptoms, compared to only one of the control patients reporting less severe symptoms and none of the open PFO group. The closed PFO group also had 10 patients (25 percent) reduce their reliance on abortive medications (plus one increasing medication use) compared to one each from the open PFO and control group.

From this study, Dr. Thaler reached four conclusions:
• Migraine is more frequent in subjects with PFO than those without.
• The majority of PFO patients with migraine have had auras.
• Percutaneous PFO closure is associated with a reduction in migraine frequency and severity, as well as with an improvement in MIDAS scores.
• Subjects used abortive migraine medicines less often after PFO closure.

Dr. Thaler adds that it is too soon to recommend PFO closure for migraine treatment at this time. However, he said it would be valuable to investigate whether or not closing a PFO could improve migraine symptoms.
PFO, Stroke and Migraine

Seeing Through the MIST

Richard B. Lipton, MD, Professor and Vice Chair of Neurology at Albert Einstein College of Medicine and Director of the Montefiore Headache Center in New York City, says he has been following the research connecting PFO and migraine with great interest.

He says the results from the recently concluded MIST trial, which was considered a failure, may be a case of the researchers setting the endpoint too high. "My thought is that PFOs are powerful migraine triggers for some people," he says. "Eliminating one very powerful trigger can make a big difference but it is not a cure. For example, if 70 percent of migraines are related to PFO, 10 percent to diet and 20 percent to menses, then PFO closure might reduce frequency by 70 percent."

Despite the disappointment some felt by the MIST results, Dr. Lipton says he views the study overall as encouraging in the sense that closure made people better on the secondary endpoints in a randomized trial. "That is good news for advocates of PFO closure," he says.

Dr. Lipton says there are two theories linking PFO closure and reduced migraine symptoms. One of these is that microemboli reach the brain and trigger migraine attacks. The other implicates a chemical trigger that bypasses the lung through a cardiac shunt. Hopefully, further research will indicate a mechanism.

While PFO closure may someday be an option to help patients with intractable migraine with aura reduce their burden, it does not seem like this option will be a complete cure. At the American College of Cardiology meeting in Atlanta in March, Peter Wilmhurst, MD of the Royal Shrewbury Hospital in Shrewbury, UK and Andrew Dowson, MD of King’s College Hospital in London, announced the results of the Migraine Intervention with StarFlex Technology (MIST) trial. This study looked at 147 patients with severe migraine who were randomized to either PFO closure using the StarFlex septal repair device (NMT Medical, Inc), a spring-loaded device implanted percutaneously via the femoral artery that occludes the PFO, or a sham procedure where the patient received general anesthesia and a groin incision to keep them blinded about whether they had closure or not. This blinding approach was needed because of the high probability of placebo effect, often seen in migraine and other pain studies. All of the patients received aspirin and clopidogrel for three months following surgery and followed up with headache specialists while remaining blinded for three months.

The primary efficacy endpoint of migraine cessation was not met. Some experts and investigators found this disappointing, while others felt this primary endpoint to be too stringent, and instead remain optimistic about this approach. There was some noticeable benefit to the procedure. The headache burden, as measured by frequency times the duration of an episode, was 136.1 before implantation and 86.06 after closure. Overall, 42 percent of the closure group had a greater than 50 percent reduction in headache days compared to 23 percent in the sham procedure arm. Complications of device placement were infrequent, but severe adverse events including cardiac tamponade did occur.

Yet the MIST study was still considered a failure, and the company’s stock prices fell sharply upon announcement of the results. The findings raise many questions among experts. If PFO is responsible for (or least contributes to) migraine, then why doesn’t closure lead to cessation? Since there is some improvement, is it possible that the closure was not complete, or are the PFO-related migraines regulated by more than one mechanism?

Hopefully, future studies will provide some answers. The MIST II trial, a US-based study with a larger population and a longer planned follow-up, is about to be launched. Further reviews of the existing data may clarify what kind of patients could benefit from this treatment. As long as future studies take into account the powerful placebo effect often associated with migraine studies, we may soon have definite data.

PFO and Stroke

The connection between PFO and stroke has received a great deal of attention in the mainstream media lately. In early 2005 pro football player Ted Bruschi of the New England Patriots suffered a minor stroke, which was later found to be directly related to PFO. Then, in December, Israeli prime minister Ariel Sharon suffered a mild stroke, also attributed to PFO, and subsequently had a brain hemorrhage related to anticoagulation therapy.

While much of the public learned about PFO from these stroke-related events, neurologists and cardiologists began to question the PFO–stroke connection in the early 1980s, when initial studies showed a higher prevalence of PFO in stroke patients. Over time it became a plausible explanation for cryptogenic stroke and TIA in the absence of other risk factors. However, there is still a major controversy over how great a risk it poses and when, if ever, closure is warranted.

One recent study (J Am Coll Cardiol 2006;47:440-445) found no increased risk of cerebrovascular events attributed to PFO after adjusting for other factors such as age and comorbidity, but an accompanying editorial questioned the techniques used. A practice parameter from the American Academy of Neurology found no compelling evidence for closure or medical therapy, and recommended that patients with cryptogenic stroke and PFO be enrolled in randomized trials comparing these options. At least two such trials are underway, including the CLOSURE-I study.
At present there are two devices available for PFO closure, and both are only available under the FDA’s Humanitarian Device Exemption for devices that can benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year: the Amplatzer PFO Occluder from AGA Medical Corporation for a non-surgical closure, and the CardioSeal Septal Occlusion System by Nitinol Medical Technologies, Inc. Both of these devices can only be used in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a PFO, and after an unsuccessful course of conventional drug therapy with warfarin (Coumadin) and aspirin.

Many centers also offer the StarFlex Occluder, NMT’s newer version of the CardioSEAL occluder, on an investigational basis as part of the CLOSURE 1 Trial. This study will randomize patients for PFO closure or medical therapy. Eligibility criteria for participants includes the patients being between 18 and 60 years of age, having had a positive study showing right-to-left shunting through PFO, and having experienced clinical TIA or stroke within the past six months.

with the StarFlex device and the RESPECT trial using the Amplatzer device. Both trials are enrolling patients between the ages of 18 and 60 years who have had a cryptogenic stroke and/or TIA within the six months prior to randomization and have a PFO identified on transesophageal echocardiography.

It will take more research to clarify the controversy, and since enrollment for such studies is often quite slow it may take some time before answers become apparent. Many patients do not want to wait, and often make a decision based on personal preference and their individual personality type. Despite the uncertainty in the existing data, some patients cannot bear the idea of “having a hole in my heart” and want it repaired, while others say, “I don’t want a device in my heart if you don’t know for sure that it works.”

In the meantime, physicians will face many PFO patients seeking treatment. At present there are no devices proven effective for preventing stroke, although two devices have humanitarian exemptions for PFO closure in very specific situations. At this point physicians must focus on treating the other risk factors, such as high blood pressure and cholesterol, and use medical therapy to treat the condition and only consider closure if medical management proves ineffective.

**Stroke and Migraine, No PFO**

Usually, the only time a vascular care specialist will see a migraine patient is when he or she is experiences an episode with focal neurologic symptoms and is concerned that it was a stroke or TIA, and the purpose of the consultation will usually be to clarify the difference between the two diagnoses. However, they are a number of patients who have a stroke or TIA and also have migraine. There seems to be a connection between the conditions, with several population-based studies showing migraine with aura is associated with an increased risk of a stroke. One particular systematic review and meta-analysis of observational studies reported in BMJ 2005;330:63-5 quantified the risk as practically doubled.

Again, the link is empirical and the actual mechanism is elusive. Part of this statistical association may be explained by conditions linked to migraine and stroke such as undiagnosed PFO, mitral valve prolapse and possibly antiphospholipid antibody syndromes.

Richard B. Lipton, MD, Professor and Vice Chair of Neurology at Albert Einstein College of Medicine and Director of the Montefiore Headache Center in New York City, says it is important to note the links between migraine treatment and stroke. For example, women who experience migraine with aura should not smoke as this has been shown to sharply increase the risk of stroke. In addition, this particular population should be warned about the small but measurable increased risk of stroke associated with oral contraceptives before taking these so they can make informed decisions.

From a practical perspective, despite these potential links, patients with both stroke and migraine are generally treated for both disorders separately. However, triptans are often avoided because of hypothetical concerns about causing cerebral vasospastic and recurrent stroke. Aspirin and many antihypertensive agents are often effective for migraine prophylaxis, and a regimen including these types of agents can treat both problems simultaneously.

**Three Mysteries, Few Clues**

Stroke specialists and pain management experts can agree that PFO presents an interesting problem. It seems this little defect of the heart may represent a missing part of our understanding of the cardiovascular system and its effects on the brain. While researchers are excited by the possibility of finding new links and new treatments, clinicians currently find themselves dealing with stroke or migraine as largely separate issues and treating with medical therapies. For now, there are few cases in stroke care where PFO closure seems warranted, and the procedure remains entirely an investigational option for migraine. Eventually, perhaps the stroke, migraine and PFO link will become more clear, and a unified treatment plan can be applied to all three disorders. PN

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