INCIDENCE OF PATENT FORAMEN OVALE IN ADULTS WITH CRYPTOGENIC STROKE OR MIGRAINE HEADACHE

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PATENT FORAMEN OVALE IN ADULTS WITH CRYPTOGENIC STROKE OR MIGRAINE HEADACHE

Abstract

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The foramen ovale is a part of normal fetal anatomy that typically closes early in life. The foramen ovale remains patent in approximately a quarter of the population. Patent foramen ovale has an increased incidence among individuals with migraine headache and cryptogenic stroke. Percutaneous closure of patent foramen ovale (PFO) is a secondary prevention measure for individuals with PFO and migraine headache or cryptogenic stroke. Results from randomized controlled trials are awaited in order to determine the safety and efficacy of percutaneous PFO closure in the treatment of migraine headache and cryptogenic stroke in comparison to the currently recommended standards of medical care. This article provides the advanced practice nurse a review of PFO anatomy and diagnostics, a review of the current science regarding percutaneous PFO closure as a treatment for stroke and migraine headache, as well as implications for nursing practice. Nurse practitioners should be advocates for their patients by coordinating with neurologists and cardiologists to ensure patients receive the most appropriate care.
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Patent Foramen Ovale in Adults with Cryptogenic Stroke or Migraine Headache

The foramen ovale is a crucial part of fetal cardiac anatomy, allowing oxygen rich blood to bypass the pulmonary circulation and directly enter the systemic circulation. The foramen ovale typically closes by two years of age, but for reasons not entirely understood, remains patent in approximately 27% of the population.\(^1\)\(^2\) Patent foramen ovale (PFO) in adults has been the focus of increased attention among the healthcare community over the past few decades. This attention has been fueled by the discovery of an increased incidence of PFO among individuals with cryptogenic stroke and migraine headache with aura.\(^3\)\(^-\)\(^6\) The major goal of current research regarding PFO is to determine the safety and efficacy of percutaneous PFO closure as a treatment option for cryptogenic stroke and migraine headache.\(^7\)

Scope and Significance

Stroke is the third leading cause of death in the United States. The annual direct and indirect costs of stroke are roughly 53 billion.\(^8\) Eighty five percent of strokes are ischemic\(^8\) and 40% of ischemic strokes are considered cryptogenic, meaning the cause is undetermined despite a comprehensive diagnostic workup.\(^9\)

Migraine headaches affect approximately 18% of women and 6% of men.\(^8\) Due to disabling pain, migraines negatively impact quality of life and result in over 157 million lost workdays in the United States annually.\(^8\) Migraine is a recurrent and chronic problem and treatments are often ineffective or can only be used for a limited amount of time.\(^8\) Recent data reveal that migraine headache, particularly with aura, is a risk factor for ischemic brain lesions.\(^10,11\)

Based on autopsy results, the incidence of PFO in the general population is approximately 27%.\(^1\) Detection of PFO in live subjects is accomplished via echocardiography or
trans-cranial Doppler. In one study, PFO was detected in 10% of control group subjects with no history of stroke,\textsuperscript{12} a significantly lower incidence than found by autopsy, revealing that PFO may not always be detectable in live subjects. PFO has been detected among 19-30\% of individuals with a history of TIA or ischemic stroke of known cause.\textsuperscript{12-14} Individuals with cryptogenic stroke have a PFO incidence between 39\% and 54\%,\textsuperscript{4,12,14,15} which is significantly higher than the general population and the ischemic stroke population. Anzola et al.\textsuperscript{5} detected PFO in 23\% of migraine headache without aura sufferers. However, PFO was detected among 48\% of individuals suffering from migraine headache with aura,\textsuperscript{5} which is significantly greater than the incidence of PFO among both the general population and individuals who suffer from migraine headache without aura. Given the deleterious effects of stroke and migraine headache, percutaneous closure of PFO represents an exciting new era in treatment.

\textbf{Literature Review}

\textit{Pathophysiology}

Patent foramen ovale is a remnant of fetal cardiac anatomy. The foramen ovale is an opening in the septum secundum, or inter-atrial wall. The septum secundum is covered by a flap-like valve, called the septum primum, which typically fuses with the septum secundum after birth. In utero, the foramen ovale allows oxygenated blood from the inferior vena cava to bypass the lungs, passing directly from the right atrium to the left atrium and entering the systemic circulation. After birth, pulmonary arterioles open, pulmonary vascular resistance drops, and left atrial pressure increases. The combined effect of these factors is what typically causes the septum primum to fuse with the septum secundum after birth, resulting in closure of the foramen ovale. When the foramen ovale remains patent, a pathway remains for blood, or emboli, to shunt directly from the right to the left side of the heart without passing through the pulmonary vasculature. Typically the PFO is a slit shaped, tunnel like defect with a variable width.\textsuperscript{2}
Atrial septal aneurysm (ASA) is an anatomic anomaly that is commonly associated with PFO.² ASA is a hyper-mobile septal wall with excursion into either the right or left atrium of 10 mm or greater.¹⁶ Although the association between ASA, PFO, and cryptogenic stroke is still debated, a meta-analysis of case control studies revealed a strong association between PFO and ASA in ischemic stroke patients 55 and younger.¹⁷ Mas et al.¹⁸ showed that the coexistence of PFO and ASA was the only factor which significantly increased the risk of recurrent cryptogenic stroke. Conversely, Homma et al.¹⁴ report comparable event rates among individuals with PFO alone versus individuals with PFO and ASA. It is important to note that the study by Homma and colleagues included patients up to age 85 and the authors recognize their findings may be misleading since association between ASA, PFO and cryptogenic stroke is strongest in patients age 55 and younger.

The mechanism by which PFO is speculated to facilitate cryptogenic stroke and migraine with aura is paradoxical embolism.⁴,⁵,¹²,¹⁹,²⁰ Paradoxical embolism is the passage of venous emboli directly into the arterial circulation, which occurs as a result of right to left intra-cardiac shunting.²¹ A PFO may allow passage of either fat emboli or thrombo-emboli into the systemic circulation.²²-²⁵ However, venous thrombosis is considered the most common culprit in paradoxical embolism despite the inability to find a definite source of venous thrombosis in the majority of patients.¹³ Right to left shunting through a PFO is either spontaneous or the consequence of provocation, such as cough or Valsalva maneuver, which causes right atrial pressure to surpass left atrial pressure, thereby inducing the right to left shunt.⁴,²⁰,²⁶

**Diagnostic Evaluation**

There are three main techniques used for the diagnostic evaluation of PFO: trans-thoracic echocardiography, trans-esophageal echocardiography, and trans-cranial Doppler. In addition to
detecting the presence of PFO, these techniques help the clinician determine the morphological features of the PFO and the degree of shunting.\textsuperscript{27}

Trans-esophageal echocardiography (TEE) is considered the gold standard for diagnosing PFO and associated right to left shunting.\textsuperscript{27,28} TEE is more sensitive than trans-thoracic echocardiography (TTE) and allows better visualization of the morphological details of the PFO.\textsuperscript{27-29} The physical opening of the PFO cannot always be visualized.\textsuperscript{2} For this reason, an injection of agitated saline contrast can be used during both TEE and TTE to determine the degree of right to left shunt.\textsuperscript{26,27} Agitated saline is a combination of saline and a small quantity of air which are mixed vigorously through a stopcock resulting in multiple micro-bubbles. The mixture is quickly injected into a peripheral vein after which the micro-bubbles can be visualized via echocardiography in the right atrium.\textsuperscript{27,28} The presence and degree of shunt is determined by counting the number of micro-bubbles, if any, that enter the left atrium within three cardiac cycles of their appearance in the right atrium, with more bubbles equaling a greater degree of shunt.\textsuperscript{15,28,30} Agitated saline is typically used in conjunction with Valsalva maneuver, which enhances the detection of right to left shunting through a PFO due to the resultant increase in right atrial pressure.\textsuperscript{26,27} The main problem encountered with TEE is the need for sedation which can limit a patient’s ability to perform the Valsalva maneuver.\textsuperscript{27} Furthermore, TEE is semi-invasive, requiring esophageal intubation, and may not be appropriate or feasible in some patients, such as stroke patients with swallowing dysfunction.\textsuperscript{28,29,31} Although TTE is the least sensitive test for the detection of PFO, it is useful for assessing cardiac morphology and function in patients with contraindication to TEE.\textsuperscript{28}

Trans-cranial Doppler (TCD) is another technique used to diagnose PFO. Agitated saline is injected in the same fashion as with echocardiography, both with and without Valsalva maneuver, followed by evaluation via trans-cranial Doppler sonography.\textsuperscript{29} TCD is preferred by
some because it demonstrates micro-bubbles originating in the venous system actually entering the arterial system and reaching target organs thereby verifying paradoxical embolism.\textsuperscript{31}

Compared to TEE, TCD has a sensitivity of 70-100\% and a specificity of > 95\% for the diagnosis of right to left cardiac shunts.\textsuperscript{32} Despite TCD's proven sensitivity and specificity for detecting moderate and large intra-cardiac shunts, TEE remains the gold standard for PFO evaluation.\textsuperscript{27,28} TEE is more sensitive, is able to visualize the physical location and size of PFO in some cases, and is able to detect other cardiac sources of emboli.\textsuperscript{28}

**Associated Syndromes and their Treatment**

PFO has been associated with a variety of clinical syndromes including cryptogenic stroke, migraine headache, decompression sickness, hypoxemia related to platypnea-orthodeoxia syndrome, and worsened high altitude pulmonary edema.\textsuperscript{12,33-36} The clinical syndromes on which this article focuses are cryptogenic stroke and migraine headache due to their greater frequency of occurrence and greater likelihood to be encountered in clinical practice.

*Cryptogenic stroke.*

Forty percent of ischemic strokes are considered cryptogenic.\textsuperscript{9} Cryptogenic stroke is diagnosed when the cause of an ischemic stroke is undetermined despite a complete diagnostic workup.\textsuperscript{37} The following should be included in the diagnostic workup: brain imaging, cardiac imaging (such as echocardiography), duplex imaging of extra-cranial arteries (carotid ultrasound), arteriography, and laboratory evaluation for a pro-thrombotic state.\textsuperscript{37} Strokes with rare causes such as arteritis, dissection, fibromuscular hyperplasia, sickle cell anemia, or lupus are not considered cryptogenic and these causes must be considered before labeling a stroke cryptogenic.\textsuperscript{9}

A patent foramen ovale is present in 39-54\% of individuals with cryptogenic stroke compared to 10-27\% of the general population and 19-30\% among individuals with stroke of
known cause.\textsuperscript{1,4,12-15} The PFO-ASA study\textsuperscript{15} compared cryptogenic stroke patients with PFO (n=267) to cryptogenic stroke patients without PFO (n=314). Patients with PFO were younger and had a lower incidence of other risk factors for stroke than patients without PFO. The study also revealed an increased incidence of ASA among cryptogenic stroke patients with PFO (19.1\%) compared to cryptogenic stroke patients without PFO (3.2\%). ASA prevalence increased as the degree of right to left shunting increased.\textsuperscript{15} The coexistence of PFO and ASA has been shown to significantly increase the risk of recurrent cryptogenic stroke.\textsuperscript{18} Large PFO size may also increase the risk of cryptogenic stroke. In a comparison of patients with cryptogenic stroke and stroke of known cause, PFO size was large in 20\% of patients with cryptogenic stroke and only 9.7\% of patients with stroke of known cause.\textsuperscript{14} A PFO was considered large if there was 2 mm or more of separation between the septum primum and septum secundum, or if 10 or more micro-bubbles entered the left atrium.\textsuperscript{14} Based on these findings, cryptogenic stroke patients that are young, have few or no other risk factors for stroke, have a large PFO, and/or have an associated ASA may be the most likely to benefit from PFO closure.

Despite the increased incidence of PFO among individuals with cryptogenic stroke, a causal relationship has not been definitively established and therefore treatment remains a highly debated issue. Current treatment options include medical management with anti-platelet or vitamin K antagonist medications, open surgical repair, or percutaneous closure.\textsuperscript{38} Percutaneous closure of PFO is accomplished via transcatheter placement of a closure device. There are multiple closure devices on the market. Device design varies but the basic structure is similar: two umbrellas, disks, or anchors are connected by a central arm, waist, or tether.\textsuperscript{7} Open heart surgery is rarely promoted solely to repair a PFO. Surgical repair is typically performed when the chest is already open for the treatment of another condition.\textsuperscript{38}
To date, no randomized, controlled clinical trials (RCT's) have been completed comparing the safety and efficacy of percutaneous closure to standard medical management. In order to compare medical management against transcatheater closure, Khairy, O'Donnell, & Landzberg\textsuperscript{16} performed a systematic review in search of studies meeting the following criteria: secondary prevention studies of percutaneous closure or medical management of PFO associated with stroke/TIA, minimum one year follow up, 10 patient minimum, and report of recurrent neurologic events. The review resulted in the inclusion of 10 studies on transcatheater closure and 6 studies on medical management. A 3.8\% to 12\% stroke or TIA recurrence rate after 1 year of follow up was revealed among medically managed patients. Patients who underwent percutaneous closure had a stroke or TIA recurrence rate of 0\% to 4.9\% after 1 year of follow up. The complete evidence to justify percutaneous closure of PFO as a treatment option for cryptogenic stroke is still awaited. Three RCT's are currently underway in the United States, RESPECT, REDUCE, and CLOSURE I, each of which compares the safety and efficacy of percutaneous closure versus standard medical therapy.\textsuperscript{38} Clinicians may wish to consult the trial websites for additional information (http://clinicaltrials.gov/ct2/show/NCT00738894, http://www.amplatzer.com/us/Respect/index.html, http://clinicaltrials.gov/ct2/show/NCT00201461).

The American Heart Association and American Stroke Association have established evidence based guidelines for the treatment of stroke/TIA in the presence of PFO based on the research available to date.\textsuperscript{39} Anti-platelet medications are considered the first line therapy for prevention of a recurrent event. Warfarin should be reserved for patients with stroke/TIA who have an additional indication for anti-coagulation. Due to lack of data, closure of PFO is not recommended after an individual's first stroke/TIA. If cryptogenic stroke/TIA recurs in spite of optimal medical therapy, then percutaneous PFO closure should be considered.\textsuperscript{39}
Heart Association, American Stroke Association, and American College of Cardiology Foundation encourage practitioners to consider referral of patients with PFO and cryptogenic stroke to the RCT's currently underway so that more definitive evidence can be established regarding the safety and efficacy of percutaneous PFO closure in the treatment of stroke.\textsuperscript{38}

\textit{Migraine headache.}

Migraine headache is an extremely common disorder, affecting approximately 18\% of women and 6\% of men.\textsuperscript{8} Migraine headaches result in significant disability and loss of productivity, account for more than 157 million lost workdays per year, and reduce functional effectiveness at work, home, and school.\textsuperscript{8} Treatment of migraine currently has three main components: avoidance of triggers, acute medical therapy, and preventative medical therapy.\textsuperscript{40} See Table 1 for a summary of the American Academy of Neurology evidence based guidelines for the treatment of migraine headache.\textsuperscript{40} Despite treatment according to these guidelines, some individuals continue to suffer from treatment refractory migraine headaches. A lack of consensus exists in regards to the definition of refractory migraine; therefore it is difficult to establish the incidence.\textsuperscript{41} Due to the disabling effect of migraine on the personal and professional lives of sufferers, it is important to develop new treatments for individuals who suffer from migraines.

PFO has been detected in 48\% of individuals who have migraine headache with aura and 23\% of individuals with migraine without aura.\textsuperscript{5} Rigatelli et al.\textsuperscript{42} performed a small, non-randomized study in which ten individuals with previous stroke and migraine headache with aura underwent percutaneous PFO closure. After the procedure all drugs for migraine were stopped. The patients were followed for a mean of 10.9 +/- 5.8 months after the procedure and all the patients were free of migraine symptoms during this time.
Table 1. Migraine headache evidence based guidelines\textsuperscript{40}

<table>
<thead>
<tr>
<th>Approach to Care</th>
<th>Treatment Recommendations</th>
<th>Specific medications</th>
</tr>
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<tbody>
<tr>
<td>Pharmacologic Preventive Therapy</td>
<td>1. Select drugs that treat co-morbid conditions if possible 2. Many preventive medications are teratogenic and should be avoided in patients who are, or may become, pregnant 3. Included drug classes are anti-epileptics, anti-depressants, beta blockers, calcium channel blockers, NSAIDS, and serotonin antagonists.</td>
<td>1. Amitriptyline 2. Divalproex sodium 3. Propranolol/timolol 4. Fluoxetine (racemic) 5. Gabapentin</td>
</tr>
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A descriptive, correlational, retrospective analysis (n=50) by Reisman et al.\textsuperscript{43} was performed to evaluate migraine symptoms among patients with previously diagnosed migraine who underwent percutaneous PFO closure for the prevention of stroke. Migraine relief was defined as complete absence of migraine symptoms, significant reduction (greater than or equal
to 50%) in monthly frequency, or minimal/no reduction (less than 50%) in monthly frequency.

Fifty six percent of patients had complete absence of migraine symptoms at a mean duration of follow up of 37 +/- 23 weeks. Additionally, 14% of patients had a significant reduction in migraine frequency, with only 30% of patients reporting minimal or no relief. There were no significant differences in migraine resolution based on the presence or absence of aura.

A third study of individuals with migraine headache undergoing percutaneous PFO closure for stroke (n=37) revealed similar levels of migraine resolution, with 76% of the patients experiencing either complete resolution or significant improvement of their migraines. Of the 37 patients studied, 24 had migraine with aura and 13 had migraine without aura. Seventy five percent of migraine with aura patients and 31% of migraine without aura patients experienced complete resolution of migraines post procedure, indicating that individuals who suffer from migraine with aura may obtain greater benefit from PFO closure than individuals without aura. These studies indicate that percutaneous closure of PFO may be an appropriate treatment for individuals who suffer from migraine headache, particularly migraine with aura.

To date, only one RCT of percutaneous PFO closure for the treatment of migraine headache, Migraine Intervention with STARFlex Technology (MIST), has been completed. Patients with frequent and refractory migraine headache with aura (n=147) were randomized to a percutaneous PFO closure procedure (n=74) or a sham procedure (n=73) in which the patient had a skin incision made at the groin. The subsequent medical management of the patients was identical. The primary end point of the study was complete migraine cessation. Secondary endpoints were incidence of migraine, severity of migraine, frequency of migraine, characteristics of migraine (presence of aura), quality of life, and change in characteristics, frequency, and severity of migraine relative to effective closure or presence of residual leak.
The results of the MIST trial were unexpected and do not support the findings of previous non-randomized studies.\textsuperscript{33} Three patients in the implant group and three patients in the sham group experienced complete migraine resolution, the primary endpoint. Secondary endpoints also did not differ significantly between groups. Exploratory analysis was undertaken to aid in hypothesis development and the design of future studies. The analysis showed that two patients in the implant group were responsible for more than one third of all migraine headache days and differed significantly from the rest of the study population. After excluding these two patients, the implant group had a 37\% reduction in median total headache days versus a 26\% reduction in the sham group.

Several issues were cited as factors resulting in the unexpected findings of the MIST trial.\textsuperscript{33} First, only patients with frequent and refractory migraine with aura were included. Treatment of these patients may be confounded by depression or other co-morbidities, making the migraine less amenable to treatment.\textsuperscript{33} Second, the primary end point of complete migraine resolution may be unrealistic, with decreased migraine frequency being a better primary end point.\textsuperscript{33} Third, PFO was measured with TTE rather than TEE which may have resulted in poor quantification of PFO size and degree of shunt.\textsuperscript{7,33} Knowledge gained during the MIST trial was influential in the design of additional, larger trials investigating the impact of PFO closure on migraine headache.\textsuperscript{7}

The data obtained to date are insufficient to determine if PFO closure is an efficacious treatment option for migraine headache. Currently, two RCT's, ESCAPE and PREMIUM, are underway in the United States to determine the efficacy and safety of percutaneous PFO closure in the treatment of migraine headache.\textsuperscript{7,45,46} Clinicians may wish to consult the trial websites for additional information (http://clinicaltrials.gov/ct2/show/NCT00267371, http://www.amplatzer.com/clinical_trials/premium_trial_amplatzer_pfo_occluder/tabid/95/default.aspx). MIST II is a
third RCT that was started and subsequently put on hold due to funding problems and difficulty recruiting patients.\textsuperscript{47} MIST III, a follow up study of the patients in MIST I, is also currently in progress in the United Kingdom.\textsuperscript{48} The results of these studies will help clarify the role of percutaneous PFO closure in the treatment of migraine headache.

Implications for Nurse Practitioners

The results of the RCT's evaluating PFO closure will be pivotal in the development of future guidelines for the treatment of stroke and migraine headache. Awareness of the appropriateness of PFO closure for a particular patient is essential so that timely referrals can be made. Currently, it is important to ensure optimal medical therapy according to established guidelines. Additionally, nurse practitioners should be highly suspicious for PFO in young stroke patients in which the cause of stroke cannot be determined despite a comprehensive workup, and in patients with migraine headache, especially if the patient experiences aura. In these scenarios, evaluation for PFO and referral to appropriate specialists should be considered. In the future, PFO closure may be recommended earlier in the treatment process.

Nurse practitioners should understand the safety profile of percutaneous PFO closure in order to have an informed discussion with patients of the risks and benefits. Whether the closure is in treatment of stroke or migraine, the post-procedural treatment is similar and therefore complications are also similar. Patients are given anti-platelets for a variable duration (6 weeks to 12 months) after implantation of a closure device in order to prevent thrombus formation on the device.\textsuperscript{16,33} Khairy, O'Donnell, & Landzberg\textsuperscript{16} performed a systematic review of percutaneous PFO closure for cryptogenic stroke/TIA and found major and minor complication rates of 1.5\% and 7.9\%. Major complications included death, massive hemorrhage, cardiac tamponade, massive pulmonary emboli, and need for surgery. Minor complications included atrial arrhythmias, minor bleeding not requiring transfusion, transient AV node block, device
fracture or embolization with successful catheter retrieval, air embolism, femoral hematoma, and asymptomatic device thrombosis. Sixteen adverse events were reported in the migraine intervention with STARFlex technology trial. Of the 16 events, 7 were definitely not caused by participation in the trial (i.e. pregnancy, sinusitis). Adverse events that were related to the procedure, device, or medications included atrial fibrillation, tamponade, pericardial effusion, retroperitoneal bleed, chest pain, epistaxis, and oozing at groin puncture site.

PFO closure for the treatment of stroke and migraine headache remains a debated and sometimes controversial treatment option. Because percutaneous PFO closure for migraine headache and stroke is still in the clinical trial stage, there are limited physicians and medical centers in the United States that provide the service. Nurse practitioners should become familiar with local or regional medical centers that provide percutaneous PFO closure. Furthermore, in order to provide accurate and up to date information to patients, nurse practitioners need to remain aware of the most current research and treatment guidelines regarding percutaneous PFO closure as a treatment option for stroke and migraine headache.

Implications for Research

The most important implication for research is the need to complete the RCT’s currently underway. This can be accomplished by providing appropriate referrals for patients with PFO and stroke or migraine headache. After optimized medical management, patients should be referred to a neurologist. Discuss with the patient and the neurologist the possibility of PFO as a cause for stroke or migraine headache and the need for evaluation and possible closure of PFO. If it is determined that PFO closure is indicated, the procedure is performed by an interventional cardiologist.

Additional implications for future research will likely be gained after completion and evaluation of the RCT’s. It will be essential to determine the particular subset of patients most
likely to benefit from PFO closure, at what point during the course of treatment PFO closure will be most beneficial, and if prophylactic closure of PFO will be indicated in any patient population.

Conclusion

Stroke and migraine headache are both potentially debilitating conditions. The potential to prevent recurrent neurologic events or accomplish complete migraine resolution with percutaneous PFO closure is an exciting possibility. It is essential to understand the current research and guidelines available regarding the treatment of stroke and migraine headache. Nurse practitioners should be advocates for their patients by coordinating with neurologists and cardiologists to ensure patients receive the most appropriate care.
References


