# Patent Foramen Ovale and Migraine Headache

David Hildick-Smith, MD, BM, BChir*, Timothy M. Williams, BA, BM, BCh

**KEYWORDS**

• Migraine • PFO • PFO closure • Migraine aura • Structural cardiology

**KEY POINTS**

- Migraine headache is a common and debilitating illness affecting a significant proportion of the population.
- The is an association of migraine headache and the presence of patent foramen ovale (PFO), with higher prevalence of migraine in patients with PFO and high prevalence of PFO in patients with migraine.
- Potential pathologic mechanisms include microemboli; fluctuations in vasoactive substances in the arterial circulation; and transient hypoxia, caused by right to left shunting in the circulation through a PFO.
- Percutaneous PFO closure has been reported to reduce the burden of migraine in patients with PFO; however, this reduction has failed to reach statistical significance in large, prospective trials.
- Further trials are warranted to explore whether a subset of patients with migraine with PFO would benefit from PFO closure.

## INTRODUCTION

Migraine is a common disorder including migraine aura and debilitating migraine headaches occurring in episodes that often significantly affect patients' lives.[1,2] Symptoms typically consist of a unilateral headache, often pulsatile, and associated other complaints such as photophobia, nausea, phonophobia, and aura. There is much debate regarding the association of patent foramen ovale (PFO) with migraine, and therefore, much discussion about potential pathologic mechanisms and possible treatments, including percutaneous closure.

Percutaneous PFO closure was first performed in 1992[3] and since then has been used for treatment of paradoxic embolization in stroke, transient ischemic attack (TIA), decompression illness, peripheral embolization, and migraine. Despite this, the role for closure in migraine has not been clearly defined because of controversy over its efficacy. This article discusses the evidence for an association between PFO and migraine, possible pathologic mechanisms, and the evidence for percutaneous PFO closure as a treatment in patients with PFO and migraine.

## MIGRAINE AND ITS ASSOCIATION WITH PATENT FORAMEN OVALE

Migraine is a common disease in the Western world, affecting around 12% of the population.[4] It is more common in women, with a male to female ratio of around 3:1, and has a peak of incidence in the middle age of life, with fewer affected in adolescence and after the age of 60 years.[1] Migraine carries a significant burden to those with the disease and significant numbers of patients miss work or school days because of the illness. One-quarter to one-third of patients have aura preceding, or during, their attacks of migraine headache. The aura can take a variety of forms of both positive and negative

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Sussex Cardiac Centre, Brighton and Sussex University Hospitals, Eastern Road, Brighton, BN2 5BE, UK
* Corresponding author.
*E-mail address:* david.hildick-smith@bsuh.nhs.uk

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neurologic symptoms. Most commonly these are visual but can cover a spectrum including sensory and motor symptoms. Typically, the aura of migraine was considered to occur before the onset of headache, but the two occur simultaneously for many migraineurs.[5]

The traditional hypothesis of migraine pathophysiology was that migraines occur because of changes in cerebral blood flow from vasodilatation and constriction; however, in recent years this has been rebuffed and the focus has turned to primary neuronal dysfunction as the underlying pathologic mechanism.[6,7]

Both the headache of migraine and the aura have been linked to a phenomenon known as cortical spreading depression.[6,8,9] Cortical spreading depression is a wave of cortical depolarization that both excites and depresses neurologic activity in its path. This phenomenon causes the aura of migraine,[10] in addition to the headache associated with classic migraine attacks. Migraine headache without aura is likely to be caused by cortical spreading depression in unconscious areas of the brain leading to headache but without conscious aura symptoms.[8]

Earlier studies suggested an increased incidence of migraine both with and without aura in patients with PFO, with a large study of patients who had cryptogenic stroke showing a significantly higher burden of migraine in patients with PFO compared with those without.[11] A cohort study in 1999 showed that the finding of a PFO, assessed by transcranial Doppler (TCD), was more common in patients with migraine with aura compared with controls.[12]

A systematic review in 2008 considered the association of PFO and migraine with a final analysis of 18 articles,[13] finding a significant association between migraine in patients with PFO, and also for the finding of PFO in patients with migraine. The association was present for both migraine with aura and migraine without aura. The findings of improved migraine symptoms in patients undergoing PFO closure in this study also supported a possible causal link between PFO and migraine. Another systematic review in 2013 also concluded that PFO and migraine were linked, and that the effect of closure was positive overall on migraine symptoms and continued to hint at a causal link.[14]

A more recent meta-analysis including 5572 patients across 21 studies was published in 2015.[15] Across all patients there was a significant association in the prevalence of migraine with aura and PFO relative to controls, with an odds ratio of 3.36 (95% confidence interval, 2.04–5.55). This association was also true for a group of patients who experienced migraine both with and without aura, but there was no significant association between patients with migraine who did not experience aura.

There are also studies showing a lack of association between PFO and migraine; however, none had the same level of evidence as a meta-analysis or systematic review. A cross-sectional study of 1101 elderly patients self-reporting symptoms of migraine failed to show a correlation between PFO and migraine,[16] with PFO assessed by transthoracic echocardiography and bubble contrast. Similarly, a case-control study with a total of 288 participants concluded that there was no increased PFO prevalence (assessed by transthoracic echocardiography and TCD) in migraineurs compared with controls.[17]

Potential explanations for differences in data include a variety of methods by which the presence of PFO is assessed, with different echocardiographic assessments between different data sets, and different thresholds at which a PFO is diagnosed.[18] There is a higher level of evidence from meta-analyses and systematic reviews to support an association between migraine with aura and the presence of a PFO than there is to refute it, but evidence of a causal link for PFO and migraine without aura is limited.

## POTENTIAL PATHOLOGIC MECHANISMS OF PATENT FORAMEN OVALE AND MIGRAINE

Two main theories have been postulated to explain a causative link between PFO and migraine, the first of which is that right to left shunt across a PFO allows microemboli and metabolites from the venous circulation to enter the systemic circulation and cause cerebral irritation. In experimental models, hypoxemia has been shown as a potential trigger of cortical spreading depression,[9] and platelet activity and aggregation have been shown to be increased in patients who get migraines, particularly around the timing of acute attacks.[19] Furthermore, studies investigating the role of aspirin and oral anticoagulation in preventing migraine attacks have yielded positive results.[20,21] These findings point toward a potential mechanism of paradoxic microemboli and localized ischemia providing a migraine trigger (Fig. 1).

Metabolites such as serotonin crossing the PFO from venous to systemic circulation has also been suggested as a cause. Serotonin is released from aggregating platelets[19] as well