INFORMATION FOR HEALTH CARE PROFESSIONALS

Patent Foramen Ovale and Migraine

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Introduction

Multiple studies suggest that migraine with aura is more prevalent in subjects with patent foramen ovale (PFO) and PFO is more prevalent in subjects who have migraine with aura. It is unclear if there is a causal relationship or simply a co-existence of these two conditions.

In utero, the foramen ovale connects the right and left atrium of the heart. After birth, when left atrial pressures exceed those in the right atrium, the foramen ovale usually closes via fusion of the septum primum and septum secundum. In approximately 25% of the general population, the foramen ovale is covered but fusion does not occur, resulting in a PFO. The PFO tunnel serves as a persistent connection that may allow for passage of blood from the right atrium to the left atrium, thus bypassing the lungs, either with each beat of the heart or only with further increases in right atrial pressure such as during Valsalva.

PFO in Migraine

PFO is found in approximately 40% to 60% of people who have migraine with aura as compared to 20% to 30% of people in the general population. A meta-analysis suggests that migraineurs with aura are more than 4x more likely to have a PFO [odds ratio 4.45] than the general population. Migraine without aura does not seem to be associated with an increase in the prevalence of PFO.

Migraine with PFO

Migraine with aura is present in about 13% to 50% of people with PFO as compared to approximately 4% of the general population. The risk of migraine with aura may be higher among those with larger PFO, right-to-left shunting at rest, and atrial septal aneurysm. Meta-analysis concludes that the odds ratio of migraine in subjects with PFO is 5.19. Available evidence to date suggests that PFO is not a risk factor for migraine without aura.

Proposed Association

It is unclear at this time if there is a causal or comorbid association between migraine with aura and PFO. A non-causal relationship is supported by the finding of autosomal dominant inheritance of large PFOs in some families. PFO and migraine could be co-inherited due to common development of endocardium, endothelium, and platelets. Alternatively, PFO may be causally

related to migraine. Passage of blood directly from the right to left atrium (bypassing the normal filtering activity of the lungs) might allow for paradoxical emboli and/or higher concentrations of serotonin, nitric oxide, kinins or other migraine precipitating chemicals to reach the brain and trigger migraine attacks. Supporting this hypothesis, a study of patients with PFO and cryptogenic stroke found that those with migraine with aura had a higher frequency of underlying thrombophilic conditions which would predispose them to paradoxical emboli. Further supporting a causal relationship, a significant increase in migraine aura attacks and development of de novo attacks has been documented in patients following PFO closure. The frequency of such attacks, likely due to thrombus formation on the closure device or platelet degranulation, is reduced after the administration of clopidogrel and aspirin.

PFO Closure

Several studies suggest that PFO closure may be an effective treatment for migraine. However, the grade of evidence from these studies is low. Meta-analyses conclude that following PFO closure, approximately 80% of migraineurs have improvement in migraine patterns, including 46%-55% who have migraine resolution Results are similar among migraineurs with and without aura. Although conclusions cannot be drawn from these low-grade studies, they provide justification for prospective, randomized, sham-controlled trials of PFO closure in migraineurs, especially in light of the inevitable off-label use of PFO closure devices for migraine treatment.

MIST was a prospective, multi-center, blinded, sham-controlled trial of PFO closure for migraine that randomized 147 migraineurs with aura. MIST failed to meet its primary end-point of complete migraine resolution 91 to 180 days post-closure (3 subjects from each group had migraine cessation) and failed to meet several secondary endpoints. A randomized controlled trial of PFO closure for migraine is currently enrolling subjects in the United States.

Conclusion

At this time, migraine should not be considered an indication for PFO screening. Patients with migraine should not undergo PFO closure for the treatment of migraine unless enrolled in a clinical trial. The potential role of PFO closure for migraine treatment will be further elucidated as results from additional clinical trials become available.

Key Points:

- Migraine with aura is more prevalent in people with a PFO.
- PFO is more prevalent in migraineurs with aura.
- Since the safety and efficacy of PFO closure in migraineurs has yet to be established, PFO closure is not recommended for the treatment of migraine.

Further Reading

1) Tepper SJ, Cleves C, Taylor FR. Patent foramen ovale and migraine: association, causation, and implications of clinical trials. Current Pain and Headache Reports 2009;13:221-226.

2) Schwedt TJ, Demaerschalk BM, Dodick DW. Patent foramen ovale and migraine: a quantitative systematic review. Cephalalgia 2008;28:531-540.

3) Butera G, Biondi-Zoccai GGL, Carminati M, Caputi L, et. al. Systematic review and meta-analysis of currently available clinical evidence on migraine and patent foramen

ovale percutaneous closure: much ado about nothing? Catheterization and Cardiovascular Interventions 2010;75:494-504.

4) Dowson A, Mullen MJ, Peatfield R, Muir K, et. al. Migraine intervention with STARFlex technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. Circulation 2008;117:1397-1404.