

EDITORIAL COMMENT

Patent Foramen Ovale Closure for Migraine Prevention

The Subject Is Still Open*

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Migraine is a common, disabling, largely inherited neurological disorder with a prevalence of 8% to 13% in the population of the Western hemisphere (1,2). The prevailing hypothesis regarding the pathogenesis of migraine is an inherited excitability of certain brain networks that, when triggered by particular endogenous or exogenous factors, leads to a cascade of events that result in head pain, in addition to a multitude of other symptoms, including a heightened sensitivity to movement and ambient light, noise, and odor; nausea; emesis; cognitive impairment; vertigo; depression; and lethargy (3). In approximately one-third of sufferers, an aura—consisting of reversible neurological symptoms such as visual illusions, unilateral paresthesias, and expressive/receptive language dysfunction—will precede or occur during some attacks. In addition, approximately 2% of the population experiences a more disabling form of migraine, known as chronic migraine, which is characterized by headache on more than 15 days/month (4).

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Case-control, meta-analytic, and population-based studies over the past decade have suggested that patent foramen ovale (PFO) is more common in migraineurs with aura and that migraine aura is more common in patients with PFO (5,6). The combination of migraine aura and right-to-left shunt (RLS) has also been shown to be a strong and independent predictor for persistent migraine (7). Retrospective and prospective studies examining the effect of PFO closure (largely to prevent recurrent presumed paradoxical embolus) on migraine suggest a benefit to PFO closure, but the grade of evidence from these studies is low (5). However, although suffering from significant limita-

tions, a single randomized sham-controlled study in the United Kingdom failed to meet its primary and secondary end points and suggested no benefit with regard to migraine outcomes in patients who underwent PFO closure (8). Although the mechanism for a potential causal relationship between PFO and migraine is not clear, recent evidence suggests that microembolization resulting in brief episodes of cerebral hypoxia/ischemia can trigger cortical spreading depression, a phenomena that is felt to be the underlying mechanism of migraine aura (9).

In this issue of *JACC: Cardiovascular Interventions*, Rigatelli et al. (10) prospectively evaluated the effect of primary PFO transcatheter closure (n = 40) with either the Amplatzer (AGA Medical Corp., Golden Valley, Minnesota) or Premere Closure device (St. Jude Medical, St. Paul, Minnesota) versus medical therapy (n = 46) on migraine disability in subjects with anatomic and functional characteristics predisposing to paradoxical embolism without previous cerebral ischemia. These characteristics included curtain pattern RLS on transcranial Doppler and transesophageal echocardiography, refractory and disabling migraine (Migraine Disability Assessment Scale grade 3 or 4), PFO, RLS at rest, atrial septal aneurysm, an acquired or inherited coagulopathy, and presence of Eustachian valve. Migraine disability was measured at months 6 and 12, and residual shunt was evaluated with contrast transesophageal echocardiography (months 1, 6, and 12) and transcranial Doppler (month 1). Subjects were also asked whether they experienced a reduction in migraine headache and aura of 100%, 50%, 25%, or 0%.

They reported, after a mean follow-up period of 29 months, complete closure in 95%—a significant reduction in migraine disability compared with those who were medically managed—and elimination of aura in all patients. Like other studies, patients with and without aura seemed to benefit from closure (27 of 32 [84%] aura subjects and 6 of 8 [75%] non-aura subjects had 50% or 100% reduction, respectively, in migraine headaches). Two patients had a persistent small shunt, and 2 subjects developed early post-procedural atrial fibrillation restored to sinus rhythm with antiarrhythmic medication. The authors concluded that the results of their study suggest that patients with anatomic and functional characteristics highly predictive of paradoxical embolism respond very favorably to transcatheter PFO closure with significant symptomatic improvement or even cure and that these characteristics might identify migraine subjects most likely to respond to PFO closure. They also speculate that the complete abolition of aura suggest that aura itself might be related to certain anatomic and functional characteristics of the right atrium.

The study is novel in the selection of patients with functional and anatomical characteristics that increase the risk of paradoxical embolism and important in that it attempts to identify a subgroup of migraine sufferers most

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likely to benefit from this procedure. The importance of identifying a patient-responsive subgroup cannot be over-emphasized, if and when PFO closure is demonstrated to be effective for migraine prevention in a well-controlled study. Given the prevalence of migraine in the population, it is critical that only those patients that are highly likely to respond be subjected to an invasive cardiac procedure with a potential for serious adverse events. The study also benefits from the appropriate inclusion of an independent neurologist to make the diagnosis of migraine with the criteria of International Classification of Headache Disorders, the careful and long-term follow-up of subjects in the study, the selection of an appropriate device based on the anatomy and dimensions of the PFO, and the absence of a history of paradoxical embolism (and presumed cerebral ischemia).

The authors appropriately outline some limitations of the study, including a small sample size from a single center that was not randomized or compared with a control group. Unfortunately, these limitations might be deal-breakers and seriously limit the ability to interpret the results of this study. The absence of a sham-control is clearly a serious limitation, whereas the lack of randomization essentially eliminates any potential for the medically managed group to serve as a “quasi-control,” because the 2 populations were very different. Indeed, the inclusion criteria seem to have been applied only to the group undergoing closure and not to the group who were medically managed. The group participants selected for PFO closure were significantly more likely to have aura, be disabled, have large shunts, and possess the functional and anatomical characteristics that increase the risk of paradoxical embolism. The ability to interpret the results is also hampered, because accurate baseline and follow-up frequency of migraine attacks, aura, and medication consumption with daily diaries were not used, as with most studies in this space. Moreover, the definition of medical refractoriness was not given, the use and duration of antiplatelet medications in either group was not addressed, and the concomitant use of prophylactic medications in the PFO closure group was not noted.

The authors conclude that, before consideration for clinical therapy, future large-scale, multicenter, randomized evaluations are needed for further confirmation of their preliminary findings. If PFO is a trigger for attacks in some patients and microembolism-induced cortical spreading depression—as suggested by recent preliminary experimental work—is the underlying mechanism, then the

high-risk characteristics used in this study to select patients for closure might indeed represent a closure-responsive subgroup. Unfortunately, although efforts have been made to complete large-scale, multicenter randomized controlled trials in the U.S., only 1 of 3 studies has remained open, largely due to enrollment proceeding at a glacial pace. Moreover, it is unlikely that the design of these trials will identify a subgroup likely to respond to PFO closure. Although this study doesn't get us closer to an answer, it keeps the subject open and might guide the selection of subjects for future clinical trials.

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