

## Patent Foramen Ovale and Migraine: Casual or Causal

Dear Editor,

The atrial septum primum and septum secundum are usually closed by the first year of age. Incomplete closure of the septum primum and septum secundum results in patent foramen ovale (PFO). On the other hand, migraine is a common condition characterized by unilateral headache associated with nausea, photophobia, and phonophobia. These two conditions may be related to each other.

Various mechanisms have been described to explain this relation. Subclinical emboli, as well as metabolites from the venous circulation bypass the pulmonary circulation through the PFO. They enter the systemic circulation and result in irritation of the trigeminal nerve and brain vasculature. This may trigger a migraine.

A small double-blind crossover study has demonstrated that aspirin, an antiplatelet drug may reduce the formation of platelet-fibrin complexes and improve a migraine. It may be possible that increased platelet activation may be a risk factor for a migraine through the action of serotonin. Transient hypoxemia resulting from shunting of blood through the PFO causes microinfarcts in the brain. It may lead to a migraine. PFO may predispose to subclinical ischemia and paradoxical embolism that may result in triggering the migraine.<sup>[1]</sup> Another study has postulated the eustachian valve, Chiari's network, and migraine with aura can be adjunctive risk factors for paradoxical embolism in the evaluation of both symptomatic and asymptomatic PFO patients.<sup>[2]</sup> It has been demonstrated that PFO is not just an example of migraine comorbidity but exerts a causal effect in the triggering of the aura by applying the criteria proposed by Bradford Hill.<sup>[3]</sup>

Epidemiologic data have shown that PFO and migraine are related. Two Italian groups were the first to report, in case-control studies, a significantly higher prevalence of PFO in subjects with a migraine with aura. They have used transcranial Doppler ultrasonography (TCD) for evaluation of patients. A study of young cryptogenic stroke patients has shown increased prevalence of a migraine in patients with PFO. A retrospective study showed that migraine

patients with PFO have higher right-to-left shunting compared to controls. In a meta-analysis of seven studies, it was concluded that there was only low-grade evidence supporting the association between PFO and migraine.<sup>[1]</sup> A study published on 2012 demonstrated that the intravenous injection of air bubbles results in bioelectrical disturbances in the brain of patients with a migraine with aura. They have large right-to-left cardiac shunts. On the contrary, this effect was absent in patients with equally large right-to-left cardiac shunts, but without a migraine. However, the majority of these patients did not experience a headache. It suggested that subclinical hypoxia-ischemia induced by paradoxical cerebral embolism was not a common cause of migraine attacks in a migraine with aura patients with large PFOs. But they may occasionally trigger aura and headache in susceptible patients, especially if the clearance of the embolus is delayed.<sup>[4]</sup>

It is quite natural that after all these studies, there was a search for the fact about whether closure of PFO can reduce migraine or not. Migraine intervention with STARFlex technology (MIST) trial is the only completed randomized double-blind sham-controlled study. It showed reduced median total migraine headache days in the PFO closure group compared to the control group.<sup>[5]</sup> Studies have demonstrated that primary transcatheter closure of the PFO resulted in a significant reduction in migraine.<sup>[6]</sup> In Percutaneous Closure of PFO in Migraine with Aura (PRIMA) trial, out of 107 participants, 53 patients were put on Amplatzer device for PFO closure. A total number of 54 patients were placed on medical therapy. There was no significant difference in migraine days per month in these two groups. But patients with PFO closure showed significant ( $P < 0.01$ ) reduction in migraine with aura attacks.<sup>[7]</sup>

There were some studies started on the relationship between PFO and migraine as well as on the effect of PFO closure on migraine.<sup>[8]</sup> But more data are required for the conclusion. It is still unclear if there is a causal relationship or simply a coexistence of these two conditions. We hope that future research works will enlighten our knowledge about this topic.

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### Conflicts of interest

There are no conflicts of interest.

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