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Editorial commentary: Can a patent foramen ovale explain why migraineurs are at an increased risk for cardiovascular disorders?

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In this issue of the Journal [1], Chen et al. nicely describe the association between migraine, particularly migraine with aura, and major adverse cardiac and cerebrovascular events. Although the underlying etiology for this association remains unclear, several hypotheses have been generated.

One hypothesis is persistent prothrombotic state. D'Andrea et al. showed that patients with migraine with aura, compared to controls, had significantly higher concentrations of basal platelet serotonin (1397 ng/10^9 platelets vs. 855 ng/10^9 platelets, $p < 0.0001$) and platelet factor 4 (4346 IU/mL vs. 3170 IU/mL, $p < 0.05$) following stimulation with platelet activating factor [2]. Tietjen et al. showed that migraineurs with a history of stroke, compared to controls, had significantly higher von Williebrand factor activity (162% vs. 108%, $p = 0.024$) and antigen (170% vs. 106%, $p = 0.002$) [3]. Migraineurs with no prior stroke showed similar findings. Martinez-Sanchez et al. showed that among 154 patients admitted for an acute ischemic stroke, hypercoagulable state was more frequent in the migraine group (38.6%, 17/44) than the non-migraine group (17.3%, 19/110) ($p < 0.01$) [4].

A second hypothesis is vasculitis. Wood et al. showed, through the use of positron emission tomography, hypoperfusion of both cortices in a posteroanterior direction (occipital to temporal and parietal) while a patient was experiencing a migraine headache [5]. The authors postulated that the arterial ischemia was a consequence of cortical spreading depression. Accordingly, migraine might be the result of a systemic vascular disorder. Sacco et al. conducted a systematic review to evaluate the endothelial and arterial function of migraineurs, and they found that the arteries of migraineurs, compared to controls, were characterized by higher augmentation index and pulse wave velocity, both of which are markers of arterial resistance [6].

A third hypothesis is the presence of a patent foramen ovale (PFO). The prevalence of PFO in the adult population is 20%–25% [7] and is increased to about 50% in patients who have migraine with aura [8,9]. A recently published meta-analysis assessing the relationship between migraine and PFO showed that patients with a PFO were more likely to have migraine with aura (OR 3.36, 95% CI 2.04 – 5.55, $p < 0.00001$) and migraine with and without aura (OR 2.46, 95% CI 1.55 – 3.91, $p = 0.0001$) but not migraine without aura (OR 1.30, 95% CI 0.85 – 1.99, $p = 0.22$) [10]. PFO has also been linked to cryptogenic stroke, myocardial infarction, peripheral embolism, and coronary artery spasm. Two different meta-analyses of 6 randomized controlled trials that assessed the efficacy and safety of PFO closure in preventing recurrent stroke showed that PFO closure, compared to medical therapy, significantly reduced the risk of recurrent stroke [11,12]. Several case reports describe patients with a PFO who had an embolic myocardial infarction [13,14]. One large study assessing the indication for transcatheter closure of PFO in 800 consecutive patients reported that peripheral embolism was the indication in 2.8% of patients [15]. We recently published a case series of 5 patients with a history of chronic chest pain, PFO, and no atherosclerosis who had angiographic evidence of coronary artery spasm. Four of these patients underwent percutaneous PFO closure and subsequently became free of chest pain and, if applicable, migraine.

These observations indicate that both migraine and PFO are associated with similar cardiovascular outcomes, which raises the question of whether the two are related. One mechanism that links these two is right-to-left shunting of prothrombotic substances (e.g., platelet aggregates and thrombi) or vasoactive chemicals (e.g., serotonin) that would normally get inactivated by the pulmonary capillary endothelium. It is therefore important for future studies assessing migraine epidemiology to evaluate the frequency of PFO. Transcranial Doppler, if available, should be utilized as the initial screening test to identify and quantitate the presence of a right-to-left shunt given that it is more sensitive than transthoracic

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echocardiography (96.1% vs. 45.1%, respectively, when compared to transesophageal echocardiogram as the gold standard) [16]. These data could potentially help us better understand the mechanism linking migraine and cardiovascular disorders.

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