Migraine and Patent Foramen Ovale: A Residual Coincidence or a Pathophysiological Intrigue?

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Abstract

Migraine is one of the most common neurological disorders and one of the most frequent primary headaches. It imposes a significant burden on the affected individuals, society and health care system. As the etiology and pathophysiology of migraine are not well understood, treatment is largely symptomatic. Patent foramen ovale is a remnant of a fetal circulation and is highly prevalent in the general population. Its presence was linked to several disorders including migraine. The aim of this review was to inquire about epidemiological and pathophysiological evidence for the coexistence of these two entities based on the available literature.

Classification and Epidemiology of Migraine

When assessing epidemiological parameters of a specific disorder, defining precise diagnostic criteria is of basic importance. The criteria of the International Headache Society provide a platform for distinguishing between different primary headache disorders. In the recent updated version of this classification, there are six major categories of migraine including migraine without aura, with aura and probable migraine (when one of the necessary diagnostic features is missing) (table 1) [1]. The complexity of the diagnosis is well illustrated by diagnostic criteria of migraine without aura. In a suspected case, there should be five or more attacks fulfilling the following criteria [2]:

Key Words
Migraine · Patent foramen ovale · Right-to-left shunting
(1) Headache attacks lasting 4–72 h and occurring <15 days per month
(2) Headache has at least two of the following characteristics:
   (a) Unilateral location
   (b) Pulsating quality
   (c) Moderate or severe pain intensity
   (d) Aggravation by or causing avoidance of routine physical activity
(3) During headache at least one of the following:
   (a) Nausea and/or vomiting
   (b) Photophobia or phonophobia
(4) Not attributed to another disorder

The importance of defining migraine was clearly shown in a meta-analysis of migraine prevalence studies, as 16 out of 58 identified studies used inadequate definitions or did not define migraine at all. Out of 24 studies included in this meta-analysis, only 5 used the International Headache Society criteria. Differences in the definition of migraine along with variation of gender and age were responsible for a striking 70% variability of prevalence rates between included studies. Prevalence of migraine in these studies depended on the case definition and varied from 13 to 20% in females, and from 8.8 and 14% in males [3].

### Pathophysiology of Migraine

Despite an important progress in biomedical sciences, the pathogenesis of migraine remains a matter of dispute. A few review papers recently summarized the contemporary concepts on the pathophysiology of migraine [4–8]. A brief outline of the pathophysiology is provided below.

Two major intracranial structures have a sensory innervation: meninges and blood vessels. The meningeal vessels are innervated by the sensory fibers of the ophthalmic branch of the trigeminal nerve. In the late eighties of the nineteenth century, migraine was viewed as a brain disorder [9, 10]. In the fifties of the last century, the so-called ‘vascular theory of migraine’ was proposed and it was further developed by other authors [11, 12]. Originally, it explained the occurrence of headache by dilatation of intracranial vessels, but recently the vasodilata-

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**Table 1. The International Headache Society and World Health Organization classification of migraine [2]**

<table>
<thead>
<tr>
<th>IHS ICHD-II code</th>
<th>WHO ICD-10NA code</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>G43</td>
<td>migraine</td>
</tr>
<tr>
<td>1.1</td>
<td>G43.0</td>
<td>migraine without aura</td>
</tr>
<tr>
<td>1.2</td>
<td>G43.1</td>
<td>migraine with aura</td>
</tr>
<tr>
<td>1.2.1</td>
<td>G43.10</td>
<td>typical aura with migraine headache</td>
</tr>
<tr>
<td>1.2.2</td>
<td>G43.10</td>
<td>typical aura with nonmigraine headache</td>
</tr>
<tr>
<td>1.2.3</td>
<td>G43.104</td>
<td>typical aura without headache</td>
</tr>
<tr>
<td>1.2.4</td>
<td>G43.105</td>
<td>familial hemiplegic migraine</td>
</tr>
<tr>
<td>1.2.5</td>
<td>G43.105</td>
<td>sporadic hemiplegic migraine</td>
</tr>
<tr>
<td>1.2.6</td>
<td>G43.103</td>
<td>basilar-type migraine</td>
</tr>
<tr>
<td>1.3</td>
<td>G43.82</td>
<td>childhood periodic syndromes that are commonly precursors of migraine</td>
</tr>
<tr>
<td>1.3.1</td>
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<td>cyclical vomiting</td>
</tr>
<tr>
<td>1.3.2</td>
<td>G43.820</td>
<td>abdominal migraine</td>
</tr>
<tr>
<td>1.3.3</td>
<td>G43.821</td>
<td>benign paroxysmal vertigo of childhood</td>
</tr>
<tr>
<td>1.4</td>
<td>G43.81</td>
<td>retinal migraine</td>
</tr>
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<td>1.5</td>
<td>G43.3</td>
<td>complications of migraine</td>
</tr>
<tr>
<td>1.5.1</td>
<td>G43.3</td>
<td>chronic migraine</td>
</tr>
<tr>
<td>1.5.2</td>
<td>G43.2</td>
<td>status migrainosus</td>
</tr>
<tr>
<td>1.5.3</td>
<td>G43.3</td>
<td>persistent aura without infarction</td>
</tr>
<tr>
<td>1.5.4</td>
<td>G43.3</td>
<td>migraine-triggered seizure</td>
</tr>
<tr>
<td>1.6</td>
<td>G43.83</td>
<td>probable migraine</td>
</tr>
<tr>
<td>1.6.1</td>
<td>G43.83</td>
<td>probable migraine without aura</td>
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<tr>
<td>1.6.2</td>
<td>G43.83</td>
<td>probable migraine with aura</td>
</tr>
<tr>
<td>1.6.5</td>
<td>G43.83</td>
<td>probable chronic migraine</td>
</tr>
</tbody>
</table>
neurogenic inflammation and the role of vasogenic peptides and vasodilatation [18]. However, the concept of local inflammation by causing extravasation of plasma and vasodilatation [18]. Originally, increased in situ inflammatory activity of tissue perfusates was demonstrated in migraineurs [15]. Recently, the serum concentration of calcitonin gene-related peptide has been demonstrated to be locally elevated at the site of pain in migraineurs [16]. This peptide, as well as others like substance P, may contribute to the development of local inflammation by causing extravasation of plasma and vasodilatation [18]. However, the concept of neurogenic inflammation and the role of vasogenic peptides are debated in the literature [19]. An integrated central neural hypothesis was postulated as an alternative explanation of the pathophysiology of migraine to the neurogenic inflammation theory [20]. This theory uses elevation of calcitonin gene-related peptide as evidence for trigeminal activation, but not inflammation. Moreover, the level of substance P was not shown to be elevated in an animal model of migraine, and substance P antagonists were not effective in relieving symptoms of migraine [16, 21]. Additionally, the central theory is consistent with recent data from neuroimaging studies [22].

An increased responsiveness of sensory terminals of the trigeminal nerve to mechanical stimuli such as vasodilatation was postulated. There is evidence from animal studies showing that exposure of the dura mater to certain substances, such as ions and inflammatory agents, and appearance of cortical spreading depression lead to activation of and sensitization to the mechanical impulses of trigeminal fibers [23, 24].

Migrainous aura was initially explained by transient vasocostriction of cortical arteries, but recently this theory has been uncrowned by tracer cerebral blood flow studies that showed occurrence of cortical hyperemia during the aura phase with ensuing oligemia during headache [25]. Another pathophysiological theory of migraine was originally proposed in the forties of the last century and was based on a concept of cortical spreading depression [26, 27]. In an animal model, a powerful wave of depolarization spreading on the cortex followed by a period of neuronal inactivity was observed. These electrical phenomena were accompanied by an increase (depolarization), and decrease (depression of cortical activity) in cerebral blood flow [28]. This hypothesis was confirmed by functional MRI in migraineous patients with visual aura. A slowly spreading increase in brain metabolic activity in the supplementary visual cortex was demonstrated, and that was followed by a reversed mirrored pattern of diminished brain activity (vasoconstriction). These changes were accompanied by positive visual phenomena, i.e. scintillations [29]. With perfusion-weighted MRI performed during the visual aura and headache phase, a decrease in cerebral blood flow was found in the visual cortex contralateral to the visual phenomena. There were no significant blood flow changes observed in patients with migraine without aura [30]. The presence of spreading depression of electrophysiological function was detected over the occipital cortex with magnetocencephalography in patients with spontaneous or induced visual aura [31]. These mechanisms were found in patients with visual aura. Whether they are the same in different types of aura remains to be elucidated.

How is it that a migraine attack starts? Briefly speaking, there are two theories explaining this phenomenon. The first and traditional one is based on a sequence of events: vasoconstriction leads to cerebral hypoxia and gives a foundation to aura. The appearance of headache is believed to be a consequence of the aura, and is probably caused by the vasodilatation first in the intracranial and later in the extracranial arteries. The other theory denies the cause-effect relation between aura and headache and focuses on parallelism of aura and headache. According to this theory, the migraine process involves spreading depression (responsible for the aura) that is accompanied by neurogenic inflammation and vascular dilatation (responsible for headache) [32].

Migraine and Comorbid Conditions

There are several disorders that are more frequent in migraineurs when compared to the general population. A recent population-based study showed an increased prevalence of chronic musculoskeletal pain (OR 1.7, 95% CI 1.5–2.1), and asthma (OR 1.6, 95% CI 1.1–2.4) [33]. Other comorbid conditions were also reported in migraineurs: depression (prevalence ratio from 2.7, 95% CI 2.1–3.5, to 4.2, 95% CI 2.0–9.2) [34, 35], panic disorder (OR 12.8, 95% CI 4.1–39.8) [35], epilepsy [36], angina pectoris due to a coronary spasm [37, 38], and mitral valve prolapse [39].
An important number of papers documented the coincidence of migraine and stroke. Migraine was demonstrated to be more frequent in female stroke patients when compared to male stroke patients, irrespectively of age. It was also shown to be more frequent in younger than older ischemic stroke patients [40]. There is evidence that migraine increases the odds for stroke about 2-fold [41, 42]. In patients younger than 35 years, the association between migraine and stroke was even stronger (OR 3.26) [42]. In young women, migraine without aura increased the odds for stroke 3-fold (95% CI 1.5–5.8), and migraine with aura 6.2-fold (95% CI 2.1–18.0) [43]. In addition, concomitant use of oral contraceptives raised the odds for stroke almost 14-fold, and smoking 10-fold [43]. When compared to controls, patients below 45 years of age with migraine had more posterior circulation lesions (55 vs. 34%, p < 0.01), in particular in the posterior cerebral artery territory (21 vs. 8%, p < 0.01) [40]. Also in older individuals with migraine, a higher load of silent brain infarcts was demonstrated when compared to controls (8.1 vs. 5%). The posterior circulation territory, particularly the cerebellum, was more frequently involved in migraineurs than in controls (5.4 vs. 0.7%, OR 7.1, 95% CI 0.9–55). Moreover, the presence of aura increased even more the likelihood of having silent infarcts when compared to controls (OR 13.7, 95% CI 1.7–112). The frequency of attacks being higher than one per month was also directly associated with an increased probability of having silent brain infarcts (OR 15.8, 95% CI 1.8–140). The same was true for silent deep white matter lesions in women. A high load of these lesions was associated with migraine (OR 2.1, 95% CI 1.0–4.1), and the risk was linked to the frequency of attacks (>1 per month, OR 2.6, 95% CI 1.2–5.7) [44]. White matter abnormalities were also demonstrated with MRI in migraineurs, but not in controls [45].

**Embryology and Epidemiology of PFO**

PFO is a residue of the fetal circulation. There are several steps of fetal heart development. First, the primary myocardial tube is formed, then comes the myocardial tube looping and formation of cardiac chambers and vascular trunks [46]. Atrial septation involves several steps, and in the final stage there are two overlapping structures namely septum primum and septum secundum [47]. Foramen ovale bypasses blood from the right atrium directly into the left atrium. In the human fetus, the venous hemodynamics privileges the flow from the ductus venosi over the flow from the inferior vena cava in passing through the foramen ovale [47, 48]. The strong blood flow with a velocity up to 85 cm/s distends the valve of the foramen ovale and forces the blood into the left atrium [48]. The volume of blood that crosses the foramen ovale equals 34% of the cardiac output at 20 weeks, and 18% at 30 weeks of pregnancy [49]. At birth, the drop of blood pressure in the right heart and opening of pulmonary blood vessels reverses the interatrial pressure gradient. A firm fusion of the septum primum and secundum should be completed by the age of 2 years [50]. However, in an important percentage of otherwise normal individuals, the closure is incomplete.

There are two milestone autopsy studies on the frequency of PFO in the general population. In the first one based on 1,100 autopsies, the incidence of PFO depended on its size; as for smaller PFO (2–5 mm), it equaled 29%, and as for larger PFO (6–10 mm), it was 6% [51]. In the second study based on 965 autopsies, the incidence of PFO was 27.3%. A progressive decline of PFO frequency from 34.3% during the first 3 decades of life to 20.2% during the 9th and 10th decades was observed. The size of the foramen ovale varied from 1 to 19 mm, but in the great majority of cases, it ranged from 1 to 10 mm in diameter. With a declining frequency of PFO with increasing age, an increase in diameter from a mean of 3.4 mm in the 1st decade to 5.8 mm in the 10th decade of life was also observed [52]. A contrast transesophageal echocardiography (TEE) study showed the presence of PFO in 9.2% of 1,000 patients referred for diagnostic TEE. It is important to notice that more than half of these patients were suspected of having a cardioembolic stroke. In this cohort, the incidence of PFO in patients in their 5th decade was greater than in those in their 8th decade (12.96 vs. 6.15%, p = 0.03) [53]. In a random general population (n = 588) aged over 45, TEE demonstrated the presence of PFO in 25.6% of studied individuals [54].

**PFO and Comorbid Conditions**

The PFO with or without coexistent atrial septal aneurysm (ASA) is generally considered to be associated with brain disorders including first-ever ischemic stroke in young patients [55, 56], cryptogenic stroke [57, 58], and cerebral decompression sickness in scuba divers [59, 60]. The presence of PFO was also described in hypobaric decompression sickness in altitude aviators and astronauts [50], platypnea-orthodeoxia syndrome [61], brain abscess [62], transient global amnesia [63], spinal
cord ischemia [64], and systemic embolization in cardiac, renal, and lower limb arteries [65–68]. Some authors do not confirm the association between isolated PFO and increased risk of ischemic stroke [69] or recurrent stroke [58, 70]. The size of the PFO and the degree of right-to-left cardiac shunt (RLS) in these disorders are debated [58, 70]. The presence of a large PFO and a high degree of RLS was demonstrated to increase the risk of cryptogenic stroke [70–73], recurrent stroke [74, 75], the number of silent ischemic brain lesions in divers [76], and cerebral decompression sickness [77]. Other studies show that either percutaneous or surgical closure of the PFO decreases the number of recurrent ischemic stroke [78, 79] as well as the number of decompression cerebral ischemic events [80], and support the positive relation between the high degree of RLS and the above-mentioned pathologies.

**PFO and Migraine**

To the best of our knowledge, there are no solid epidemiological data on the coexistence of atrial septal abnormalities and migraine. The only available information comes from case-control studies and randomized trials, which in the majority were not planned to evaluate the questioned hypothesis. One of these studies included 581 young patients with cryptogenic ischemic stroke to assess the frequency of recurrent cerebral ischemic events in relation to the presence of PFO and/or ASA. In the baseline characteristics, a significant difference in the frequency of migraine, defined according to international criteria [2], between patients without and with atrial septal abnormalities (PFO, ASA or both) was found (13.5% vs. 27.4%, p < 0.001). The odds for those with atrial septal abnormalities to have migraine were 1.96 (95% CI 1.24–3.12) [58]. In a population-based study, migraine was found in 20% of 140 unselected young cryptogenic ischemic stroke patients with PFO [81]. Others, in a cohort of 74 cryptogenic stroke patients, found PFO in 59% of cases. A history of migraine with aura was more frequent in patients with PFO than in those without (28.5% vs. 13%, p = 0.03) [82]. Another case-control study included 113 patients with migraine with aura, 53 with migraine without aura, and 25 matched nonmigraine controls. PFO was found in 48% of patients with aura, 23% of those without aura, and in 20% of controls. The odds for having PFO in patients with aura when compared to those without were 3.13 (95% CI 1.41–7.04, p = 0.002), and when comparing patients with aura with controls, the odds for having PFO were 3.66 (95% CI 1.21–13.25, p = 0.01). There was no significantly increased risk of having PFO comparing patients with migraine without aura and controls (OR 1.17, 95% CI 0.32–4.45). Moreover, a higher prevalence of RLS at rest, as assessed with transcranial Doppler (TCD), was demonstrated in patients with aura (7%) when compared to those without (1.8%) [83]. When 44 patients with migraine with aura were compared with 73 young ischemic stroke patients and 50 controls, the prevalence of RLS was demonstrated with TCD in 41% of migraineurs and in 8% of controls (RR 3.2, 95% CI 1.4–7.2, p < 0.005). There was no significant difference in the frequency of RLS between cases and patients with ischemic stroke (41 vs. 35%, RR 1.2, 95% CI 0.5–2.6). No difference in the degree of RLS was demonstrated between groups [84]. In a recent paper, 122 patients with migraine (62 with aura) and 65 controls were evaluated with TCD for the presence of RLS through the PFO. PFO was more frequent in patients with aura (53%) than in those without aura and in nonmigraine controls (25% in both groups, p < 0.05) [85]. There is one study on the prevalence of ASA in patients with migraine. One of the very interesting findings of this work is that the prevalence of isolated ASA was significantly higher in patients with migraine with aura than in those without aura and controls (28.5 vs. 3.6 vs. 1.9%, respectively) [86]. At this stage, the evidence in favor of a cause-effect relationship between PFO and migraine seems to be weak if not circumstantial. Interpretation of the results of the above-mentioned studies is quite difficult, as either they were not planned to seek for the correlation between migraine and PFO and included cryptogenic stroke patients [58, 81] or the numbers of patients studied in a case-control manner were small. Although data from prospective population-based studies are lacking, the recent literature stresses an important connection between the occurrence of PFO and migraine, especially migraine with aura [44, 87].

Fortuitously, trials testing the effectiveness of atrial septal defect closure in various groups of patients showed some effect on the frequency and quality of migraine attacks in post hoc or retrospective analyses. Recently, the results of most of these studies have been the subject of a critical editorial [88]. The results of these trials are summarized in table 2. These studies included 842 highly heterogeneous patients with more than half of them with a cryptogenic stroke or transient ischemic attack (TIA) attributed to paradoxical embolism, or other disorders including decompression sickness, peripheral embolism and desaturation. Neither of these studies included patients with isolated migraine as an indication for percu-
taneous PFO closure. In total, 237 studied patients had a history of migraine. When taking into account all the results, a complete resolution of symptoms was seen in approximately 40%, and improvement of migraine symptoms in 43%. The mean follow-up ranged from 6 to 24 months. Half of the studies did not report any periprocedural and postprocedural complications. In those that did, periprocedural atypical migraine symptoms, coronary artery air embolism, TIA, and paroxystic atrial fibrillation were reported. There was one case of fatal pulmonary embolism. What is of note, in all of these studies, aspirin, a combination of aspirin and clopidogrel or anticoagulants alone were given as a preventive treatment for a maximum of 6 months in various doses according to the local experience. Interpretation of these results should be done with caution, as these studies were based on small groups of patients, they were mostly retrospective, and methods used for migraine screening were not standardized. Moreover, these studies were not blinded, and the 40% difference in frequency and in quality of migraine attacks in relation to interventional treatment can be in large part due to the placebo effect. Last but not least, the majority of the patients received antiplatelet agents, which may influence the frequency and intensity

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Atrial septal defects</th>
<th>Type of patients</th>
<th>Migraine before closure, %</th>
<th>Resolution/improvement of migraine, %</th>
<th>Complications (periprocedural/long-term), %</th>
<th>Mean follow-up months</th>
<th>Postprocedural prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilmshurst et al. [117]</td>
<td>retrospective</td>
<td>32 PFO, 5 ASD</td>
<td>29 DS, 4 significant RLS, 4 IS</td>
<td>57</td>
<td>48/38</td>
<td>30&lt;sup&gt;1&lt;/sup&gt;</td>
<td>17</td>
<td>aspirin 150 mg (6 months)</td>
</tr>
<tr>
<td>Onorato et al. [118]</td>
<td>prospective</td>
<td>256 PFO (86 ASA)</td>
<td>101 IS, 144 TIA, 17 PE, 8 other&lt;sup&gt;2&lt;/sup&gt;</td>
<td>10.5</td>
<td>0/100</td>
<td>9&lt;sup&gt;3&lt;/sup&gt;/2&lt;sup&gt;4&lt;/sup&gt;</td>
<td>19</td>
<td>aspirin or anticoagulants (6 months)</td>
</tr>
<tr>
<td>Morandi et al. [119]</td>
<td>prospective</td>
<td>17 PFO</td>
<td>8 MA, 9 M</td>
<td>100</td>
<td>29/59</td>
<td>12&lt;sup&gt;5&lt;/sup&gt;</td>
<td>12</td>
<td>aspirin 150 mg (6 months)</td>
</tr>
<tr>
<td>Post et al. [120]</td>
<td>retrospective</td>
<td>66 PFO</td>
<td>61 IS, 3 PE, 2 other&lt;sup&gt;6&lt;/sup&gt;</td>
<td>36</td>
<td>84/NA</td>
<td>NS</td>
<td>6</td>
<td>aspirin</td>
</tr>
<tr>
<td>Schwerzmann et al. [121]</td>
<td>retrospective</td>
<td>215 PFO</td>
<td>175 IS/TIA, 13 PE, 26 DS</td>
<td>22</td>
<td>NA/83</td>
<td>NS</td>
<td>24</td>
<td>clopidogrel 75 mg and aspirin 100 mg (1 month), followed by aspirin 100 mg (6 months)</td>
</tr>
<tr>
<td>Azarbal et al. [122]</td>
<td>retrospective</td>
<td>26 ASD, 76 PFO (24 ASA)</td>
<td>IS&lt;sup&gt;7&lt;/sup&gt;, ASD</td>
<td>42</td>
<td>60/16</td>
<td>NS</td>
<td>6&lt;sup&gt;8&lt;/sup&gt;</td>
<td>aspirin or clopidogrel</td>
</tr>
<tr>
<td>Reisman et al. [123]</td>
<td>retrospective</td>
<td>162 PFO</td>
<td>162 IS</td>
<td>35</td>
<td>56/14</td>
<td>NS</td>
<td>12&lt;sup&gt;9&lt;/sup&gt;</td>
<td>clopidogrel 75 mg (3 months), followed by aspirin 325 mg (6 months)</td>
</tr>
<tr>
<td>Mortelmans et al. [94]</td>
<td>retrospective</td>
<td>75 ASD</td>
<td>ASD</td>
<td>30</td>
<td>45/0</td>
<td>NS</td>
<td>29</td>
<td>NS</td>
</tr>
</tbody>
</table>

ASD = Atrial septal defect; DS = decompression sickness; IS = ischemic stroke; NS = not stated; PE = peripheral embolism; MA = migraine with aura; M = migraine without aura; NA = not applicable.

<sup>1</sup> New or unusually frequent periprocedural fortification spectra.

<sup>2</sup> Patients with platypnea-orthodeoxia syndrome, 1 with refractory hypoxemia, 3 scuba divers, 2 patients with thrombophilia.

<sup>3</sup> Including 4% of coronary air embolism, 5% of femoral hematomas, 0.4% of cardiac tamponade.

<sup>4</sup> Including 0.8% of fatal pulmonary embolism and 0.8% of TIA.

<sup>5</sup> Periprocedural atrial fibrillation.

<sup>6</sup> One case of brain embolism, and one of desaturation.

<sup>7</sup> Exact numbers not stated.

<sup>8</sup> Follow-up available for 92% of patients.

<sup>9</sup> Seven patients with migraine lost to follow-up.
of migraine headaches [89, 90]. Three recent papers seem to contradict the results of the above-mentioned studies. One of them reports an asymptomatic patient that underwent atrial septal defect closure with an Amplatzer septal occluder device complicated in the postprocedural period by new-onset attacks of migraine with aura [91]. The other case report was similar and presented a patient with a history of migraine with aura that underwent a percutaneous closure of asymptomatic atrial septal defects with the same type of device. This patient experienced an aggravation of his headaches in the 6 months following percutaneous closure of his atrial septal defects [92]. Moreover, the frequency and severity of migraine attacks were shown to be diminished by the presence of cardiovascular risk factors and TIAs [93]. The most recent, retrospective study reports the effects of atrial septal defect closure with an Amplatzer occluder on migraine frequency in an unselected group of 75 patients. During a mean follow-up of 29 months after closure, the authors found a 50% decrease in the prevalence of migraine with aura, and a 43% decrease in migraine without aura (45% in total). However, there were 3 patients with new-onset migraine without aura, and as much as 7 patients with new-onset migraine with aura during the follow-up, which renders the results of this study equivocal [94].

At this point, we can discuss whether the RLS can be the source of migraine headache or aura, or both. As in the case of cryptogenic stroke, the proposed mechanism of migraine is paradoxical embolism that may lead to hypoperfusion in the territory of transiently occluded brain artery, thus producing focal neurological symptoms. As data from the literature show, patients with visual aura experience a transient hypoperfusion in the occipital cortex [29]. Interestingly enough, in patients with PFO, a preference for the emboli to lodge in the posterior circulation was also shown [95, 96]. Moreover, in patients with frequent attacks of migraine with aura, the odds for having subclinical posterior territory infarcts were increased almost 16-fold [44], and in young patients with migrainous stroke, a predilection for posterior circulation lesions was shown [40]. The results of studies showing increased platelet aggregability in patients with migraine support the presumed paradoxical embolic etiology of migraine [97, 98]. Furthermore, both antiplatelet agents and anticoagulants were shown to decrease to some extent the frequency of migraine attacks [89, 90, 99, 100]. The occurrence of migraine was linked with prothrombotic states such as antiphospholipid syndrome [101, 102], factor V Leiden mutation and protein S deficiency [103], hyperhomocysteinemia [104], and methylenetetrahydrofolate reductase TT677 genotype [105, 106]. In addition, the migraineurs were shown to have increased levels of prothrombin factor 1.2 compatible with the activation of clotting cascade [107]. Most of these correlations were the subject of a recent review [108]. A very interesting positive correlation between the occurrence of migraine and the presence of PFO in patients with genetically proven CADASIL (cerebral autosomal dominant angiopathy with subcortical infarcts and leukoencephalopathy) has recently been demonstrated. This finding points toward a common genetic or developmental disorder (e.g. endothelial dysfunction) for these three clinical entities [109]. Embryological data also seem to point toward a common denominator for migraine and atrial septal defects. In chicken ventral hindbrain neural tube, a group of pluripotent cells, the so-called ventrally emigrating neural tube cells, is responsible for the formation and development of the heart including atria and interatrial septum. Extirpation of these cells prior to their departure resulted in different malformations of the heart including atrial septal defects [110]. A similar group of cells was shown to emigrate at the site of attachment of the trigeminal nerve to populate the mesenchyme of the first pharyngeal (branchial) arch, as well as to form the trigeminal ganglion [111, 112]. One can speculate that a developmental dysfunction of this process may cause both atrial septal defects and a tendency toward an abnormal functioning of the trigeminal nerve system. The activity of the latter was shown to be increased during migraine attacks [16, 18].

Apart from paradoxical embolism and endothelial dysfunction, another mechanism related to cardiac RLS may be hypothesized. Some authors demonstrated an oxygen desaturation (venous blood shunting) in patients with PFO as determined with ear oximetry [113]. However, others did not confirm these results by arterial blood analysis [114]. What about other types of shunting? Normally, before entering the arterial bed, the blood passes through the lungs, which extract and metabolize many substances including biogenic amines such as serotonin [115]. In cases of persistent RLS or during Valsalva maneuver, one can imagine that part of these vasoactive substances could escape the pulmonary metabolism, thus causing 'metabolic RLS', and directly enter the arterial circulation activating platelets, or exerting their action on cerebral vasculature. One study demonstrated a disruption of pulmonary metabolism of norepinephrine in patients with cardiac RLS, and suggested a correlation between the degree of RLS and the arterial levels of norepinephrine and serotonin [116]. Some authors consider...
migraine as a chronic sympathetic nervous system disorder, and show that migraineurs have reduced supine plasma norepinephrine levels, peripheral adrenergic receptor supersensitivity, and suboptimally adjusted plasma norepinephrine levels in response to physiological stress [7].

The lack of clear-cut epidemiological data, the existence of contradictory results of pathophysiological and therapeutic studies, difficulty in differentiating migrainous aura from TIA all reflect the complexity of the questioned correlation between PFO and migraine. There are several hypotheses, of which the most popular and industry-stimulating one is that of paradoxical embolism. For some health care professionals, the interventional closure of this hole in your heart that gives you headaches, and may cause stroke, or do you prefer to close it with this little and very modern device?” However, we shall rather wait for more reliable data.

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References


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