SHORT COMMUNICATION

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# Advances in the Study of the Correlation Between Patent Foramen Ovale and Migraine

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**ABSTRACT**

This article examines the relationship between patent foramen ovale (PFO) and migraine, emphasizing the mechanisms underlying the connection and the historical status of transcatheter PFO closure as a treatment for migraine. Patent foramen ovale is the most prevalent congenital cardiac defect in adults and frequently co-occurs with migraine, particularly migraine with aura. This article reviews several studies that have identified a significant prevalence of PFO in patients with migraine, implying that PFO and migraine may be more closely associated than previously thought. The underlying mechanisms of this association involve the transfer of emboli from the venous system to systemic circulation through the PFO, which can result in a range of clinical conditions. Transcatheter PFO closure therapy has demonstrated benefits in some patients with migraine; however, additional research is required to determine its effectiveness and safety. This article offers a comprehensive review of the current understanding of the link between PFO and migraine and emphasizes the need for further research in this field.

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## INTRODUCTION

The foramen ovale is a common anatomical feature of the atrial septum of the fetal blood circulation system. It is a channel that bypasses inactive and high-resistance pulmonary circulation, allowing the mother's oxygen and placental blood to directly reach the fetus's left heart system typically observed in the middle atrial septum. After delivery, there was a decrease in pulmonary vascular resistance, the pressure of the right heart system decreased, the pulmonary venous blood return increased, and the pressure of the left heart system gradually increased, pushing the primary and secondary septa closer and allowing for adhesion and fusion. The foramen ovale closes functionally, forming the permanent atrial septum. Patent foramen ovale (PFO) is a condition in which the foramen ovale does not close beyond 3 years of age.[1] Patent foramen ovale is a prevalent congenital heart disease among adults, with an occurrence rate of 15%-35%.[2] Various methods can be used to examine PFO (Table 1). Based on its diameter, it can be divided into small (<1.9 mm), medium (2.0-3.9 mm), and large (>4 mm) PFO.[3] As shown in Table 2, PFOs can be classified as simple or complex. Such a tiny atrial septal fissure did not cause significant hemodynamic changes; however, as medicine has advanced, numerous studies have revealed that emboli can pass from the venous system to the systemic circulation via the PFO, leading to various conditions. Evidence supporting this notion is derived from cardiac imaging and autopsy case series, which have captured blood clots of diverse sizes and configurations moving through PFO tunnels or lodged within them.[4]

Migraine is a prevalent and debilitating neurological condition characterized by recurring intense headaches and temporary neurological and systemic symptoms. They are recognized as one of the most common and severe medical issues[5] worldwide and are typically associated with migraines, including photophobia, phonophobia, cutaneous allodynia, and gastrointestinal issues such as nausea and vomiting.[6] The World Health Organization classifies migraine as the third most prevalent illness and second most prevalent neurological condition globally. According to estimates, the prevalence of migraine in the general population over the course of a year is 12%.[7-8] The prevalence rates for women per year and for their entire lives are 18% and 33%, respectively, while for men, these

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**Table 1.** Comparison of each method for examining patent foramen ovale[35]

| Methods | Advantages | Disadvantages | Specificity | Sensitivity | Remarks |
|---|---|---|---|---|---|
| TTE | ① Safe, non-invasive, and easy to operate;<br>② Can demonstrate the structure of the heart. | ① Susceptible to interference by obesity, lung gas, thoracic motion, etc.;<br>② low detection rate of PFO;<br>③ difficult to accurately measure the size of PFO. | 99% | 46% | The most used method of examining PFOs. |
| TEE | The atrial septum and the size and shape of the PFO can be clearly discerned using this technique | ① Semi-invasive examination;<br>② esophageal lesions, cardiopulmonary failure, advanced age, etc. are contraindications. | 92% | 89% | The "gold standard" and preferred method for diagnosing PFO. |
| cTTE | ① Safe and non-invasive;<br>② Check whether there is RLS, and grade RLS According to the count of microbubbles observed in the left heart chamber;<br>③ Can determine the source of RLS according to the time of microbubble development in the left heart cavity. | Influenced by many factors, repeated examination of RLS has some differences. | 82% | 88% | More accurate in quantifying shunts than cTCD. |
| cTEE | ① Check the presence or absence of RLS and grade it based on the number of microbubbles seen in the left heart cavity, utilizing American English grammar, spelling, and terminology;<br>② Can accurately determine the source of RLS. | ① Semi-invasive examination;<br>② esophageal lesions, cardiopulmonary failure, and advanced age are contraindications. | 91.4% | 89.2% | Difficult for silver subjects to effectively complete the Vaudeville maneuver; RLS detection rate and shunt detection are less than cTTE. |
| cTCD | RLS grading can be determined by observing how many air bubbles appear in the cranial circulation. | ① Cannot show the morphological structure of the heart;<br>② difficult to distinguish the origin of RLS. | 92% | 94% | Highest sensitivity; preferred method for PFO screening. |

The table demonstrates the association method used during the examination of patent foramen ovale (PFO) using cardiac imaging for diagnostic purposes. These techniques include transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE), which offer valuable insights into the cardiac function and structure. In addition, contrast transthoracic echocardiography (cTTE) and contrast transesophageal echocardiography (cTEE) enhance visualization by introducing contrast agents. Furthermore, contrast transcranial Doppler sonography (cTCD) is used to assess cerebral blood flow, particularly in conditions such as stroke. Each technique plays a crucial role in comprehensive evaluation of cardiac and cerebrovascular health.

figures are 6% and 13%, respectively.[5] Furthermore, the worldwide prevalence of migraine (which affects 14.7% of the population) places a significant strain on public health systems.[9] Current treatments for migraine primarily involve medication, which can sometimes be ineffective or difficult to tolerate.[10]

Recently, a multitude of studies have discovered a strong association between PFO and migraine and have sought to benefit migraine patients through transcatheter PFO closure. This research examines the connection between PFO and migraine, the underlying mechanisms of their interrelation, and the history and current state of transcatheter PFO closure therapy (Tables 1 and 2).

### MAIN POINTS

- Patent foramen ovale (PFO) is the most frequently observed congenital cardiac defect among adults.
- Patent foramen ovale is significantly associated with migraine, particularly when accompanied by aura.
- Several studies have consistently demonstrated a considerable prevalence of PFO among individuals with migraines. According to various reports, patients with migraines often exhibit a high prevalence of PFO.
- Possible mechanisms linking PFO and emboli transfer include venous to systemic circulation.
- Transcatheter PFO closure therapy has been found to benefit some patients with migraine; however, more research is needed to determine its effectiveness and safety.

## CORRELATION BETWEEN MIGRAINE AND PATENT FORAMEN OVALE

In 1998, Del Sette et al[11] first established a correlation between PFO and migraine. In 1999, Ansola et al conducted a study in which they compared 113 patients with migraine with aura (MA), 53 patients with migraine headache (MO) without aura, and 25 healthy controls. The results showed that 48% of MA subjects had PFO, which was significantly higher than the rates in the MO and healthy control groups. The difference between the MO group (23%) and healthy control group (>20%) was not significant, implying that MA and PFO have a stronger association than MO.[12] A meta-analysis conducted by Schwedt et al[12] (2008) demonstrated that the prevalence of PFO in patients with migraine varied from 39.8% to 72%. Additionally, the prevalence of migraine in patients with PFO has been reported to be between

**Table 2.** Comparison of Characteristics of Simple and Complex Patent Foramen Ovale[5]

| Simple PFO | Complex PFO |
|---|---|
| Short length (<8 mm)<br>No ASA<br>No excessively long inferior vena cava valve or Chiari mesh<br>No hypertrophic secondary atrial septum (≤10 mm)<br>No concomitant atrial septal defect (ASD) | Long tunneling type (≥8 mm)<br>Complicated ASA<br>Excessively long inferior vena cava valve or Chiari mesh<br>Secondary septal over thickness (>10 mm)<br>Complex lesion type<br>Multiple outlets on the left atrial side<br>Anatomical abnormalities because of aortic root dilatation |

The table compares the characteristics of simple and complex patent foramen ovale (PFO) with atrial septal aneurysm (ASA) and atrial septal defect (ASD). This analysis provides insights into the differences between these cardiac conditions, aiding in understanding their pathophysiology, and guiding personalized treatment strategies for better patient outcomes in cardiovascular medicine.

22.3% and 64.3%. In 2018, a multicenter, case-control study examined the prevalence and severity of restless legs syndrome (RLS) in Chinese patients with migraine. This study demonstrated a considerably higher prevalence of RLS in MA and MO patients (63.8% and ~40%, respectively) than in healthy controls (29.4%), particularly when RLS shunts substantial fielded.[13] According to a report by Kumar et al[14] in 2019, the prevalence of MA accompanied by PFO was found to be between 40% and 60% as opposed to only 20%-30% in the general population. In 2021, the First Clinical Medical College of China Three Gorges University reported a higher prevalence of RLS in the MA group (48.38%) than in the MO (35.98%) and control (23.64%) groups.[15] In comparison, a prospective case-control study carried out by Eren et al revealed no statistically substantial discrepancy between the occurrence of PFO in the migraine group (n=203) and healthy control group (n=212) (42% vs. 44%, *P*=.61). This finding implies that the prevalence of PFO was comparable in migraine patients with and without aura (41% vs. 42%, *P*=.87).

Most trial outcomes indicate a strong relationship between PFO and migraine; nevertheless, some trial results exhibit significant inconsistency. The conclusions need to be more consistent and the relationship between the 2 needs to be further demonstrated.

The connection between MA and a higher risk of ischemic stroke in young individuals, particularly women, has been firmly established in numerous studies. Research has indicated that relative risks range from 2.28 to 6.2, which additionally reinforces this association.[16] Moreover, it is important to mention that approximately 40% of ischemic strokes in women with migraine aura occur following migraine attacks. Additionally, the presence of a patent foramen ovale (PFO) in migraineurs with aura may add to this increased risk.[17] Considering these results, it is critical to acknowledge the connection between MA and ischemic stroke in young patients in both clinical practice and future research, as studies have demonstrated a strong correlation between MA and ischemic stroke.

## MECHANISMS ASSOCIATED WITH PFO INDUCING MIGRAINES

Despite extensive research, the precise relationship between PFO and migraines remains unclear. Four theoretical hypotheses have been proposed to explain the potential connection between PFO and migraine: microemboli-triggered cortical spreading depression, vasoactive substance hypothesis, impaired cerebral autoregulation, and a common genetic basis.[18] Although the relationship between PFO and migraine remains a subject of ongoing debate, some studies have indicated a considerable connection, while others have failed to find any significant association or link between small- or moderate-sized PFOs and migraines.[19] Although it remains unclear how PFO is linked to migraine and whether there is a causal relationship, evidence supporting such a connection is insufficient. Furthermore, studies on the frequency and extent of right-to-left shunts in migraine patients with PFO have produced inconclusive results.[20-22] Further studies are necessary to arrive at a consensus regarding the precise mechanism and causal relationship between PFO and migraine.

### Vasoactive Substance Hypothesis

In healthy individuals, the metabolite serotonin or 5-hydroxytryptamine (5-HT) of the venous system first enters the pulmonary circulation, is degraded by monoamine oxidase (MAO), and is then excreted in the urine. In patients with PFO, some 5-HT enters the systemic circulation directly through the right atrium and enters the brain to stimulate the trigeminal nerve and cerebral vessels, thereby causing migraine.[23] Other metabolites such as nitric oxide, kinin, and endothelin can also cause headaches by increasing 5-HT levels. According to a recent study, the levels of peripheral blood 5-HT decreased by 27.27% in patients who underwent PFO closure during follow-up, while no significant change was observed in patients who received only drug treatment (*Pp*=.0034). These findings imply that PFO closure may increase 5-HT levels in vivo.

### Paradoxical Embolism Hypothesis

Cortical spreading depression (CSD) is a condition linked to migraines in individuals with PFO. These patients experience increased pressure within the right atrium of the heart during activities, such as coughing, diving, or performing the Valsalva maneuver. Thus, there is a high chance that microemboli (air/fat) can enter systemic

circulation directly through the PFO without pulmonary circulation filtration, resulting in cerebral arteriolar occlusion that causes hypoperfusion and triggers CSD. The brain slowly spreads depolarized fluid to the adjacent cortex. This can lead to migraine.[24] Wilmshurst et al[25] observed 200 divers with decompression sickness and found that patients with severe restless leg syndrome (RLS) had more venous bubbles entering their systemic circulation during diving, and their degree of multiagent lung syndrome (MALS) increased after diving, indicating that RLS might play a role in the etiology of MALS and that its mechanism is related to abnormal gas embolism.

### Transient Hypoxemia

Large amounts of venous blood from the right heart and venous system enter the left atrium through the PFO and mix with oxygenated arterial blood, resulting in transient locoregional hypoperfusion that directly triggers migraine symptoms in the central nervous system.[26] However, patients with PFO may have a higher likelihood of experiencing migraines with visual aura owing to reduced blood flow to the occipital cortex, which is believed to be significantly greater than that in the general population.

### Genetic Factors

In 2004, Wilmshurst et al, who tracked 20 patients with atrial septal defects or PFO, found that 71 of their offspring had similar abnormalities, matching the autosomal dominant inheritance probability. The frequency of first-degree relatives with PFO combined with aura migraines was as high as 70%. This is the first report to show a correlation between PFO inheritance and aura migraine.[27] In 2008, Zikari et al observed that patients (n = 23) with autosomal cerebral artery disease with subcortical infarction and leukoencephalopathy caused by mutations in the NOTCH3 gene. Cerebral infarction, dementia, and migraine were the main symptoms, 71% of which were RLS, and they NOTCH3 gene played a crucial role in regulating the morphology of the heart valves and diaphragms during embryonic development, reflecting the possible genetic correlation between migraine and PFO.

### Studies of Transcatheter PFO Closure for PFO Complicated With Migraine

In view of the high correlation between migraine and PFO, there are few reports of PFO and migraine treatment with transcatheter PFO closure. Wilmshurst et al first reported the effect of transcatheter PFO closure in patients with migraine in 2000. Although the trial results are controversial, this study provides new ideas for the treating migraine.[28] Since then, numerous clinical studies have investigated the effectiveness of transcatheter PFO closure in migraines: (i) The Migraine Intervention with STARFlex Technology (MIST) trial was the world's inaugural randomized, double-blind, sham-controlled clinical trial on PFO closure in migraines. In this study, 147 adult patients with migraine who experienced fewer than 5 attacks per month and had moderate-to-severe restless legs syndrome were enrolled. These patients did not show any improvement with at least 2 preventive drug treatments. The individuals were assigned to either the group receiving the STARFlex occlusion device treatment or the sham group. All patients were administered oral aspirin and clopidogrel as antiplatelet therapy from 24 h before surgery until 90 days after surgery, and they were monitored for 6 months following the surgical procedure. There was no noticeable difference between the occlusion and sham groups with respect to the primary endpoint of ceasing migraine 91-180 days after surgery. The results showed a 4.05% (3/74) success rate in the occlusion group, which was similar to the 4.11% (3/73) success rate in the sham group, with no statistically significant difference ($P = .51$). The study reported a significant reduction in the number of migraine attack days after excluding 2 outliers with a $P$-value .027.[29] (ii) In a separate multicenter randomized trial, the PRIMA (Percutaneous Closure of PFO in Migraine (PRIMA) procedure was executed on 83 adult patients who experienced 3-5 days of acute migraine symptoms each month, lasting for ≤14 days. The objective of this study was to evaluate the effect of Amplatzer PFO Occluder therapy on the number of monthly migraine episodes for a 9- to 12-month period post-randomization and to compare it to the 3-month baseline phase prior to randomization. Participants were randomly assigned to either PFO closure or medical treatment. Both groups received 75-100 mg/day acetylsalicylic acid for 6 months and 75 mg/day clopidogrel for 3 months. A total of 107 patients were randomly divided into 2 groups, with 53 patients receiving the Amplatzer PFO Occluder and 54 patients receiving medical management. A total of 83 patients, consisting of 40 occluders and 43 controls, successfully completed the 12-month follow-up period. The average number of migraine days at baseline was 8 (±4.7 SD) for the occluder group and 8.3 (±2.4) for the control group). The primary outcome failed to show a significant difference, with a reduction of −2.9 days in the PFO closure group compared to −1.7 days in the control group ($P = .17$). Five transient adverse events related to PFO closure were observed. (iii) The PREMIUM trial was a double-blind, randomized clinical study involving patients aged 18-65 years with frequent migraines (6-14 days per month) that persisted despite treatment with at least 3 medications. The purpose of this study was to evaluate the effectiveness of the Amplatzer PFO Occluder in reducing migraine frequency compared to standard medical management. Many individuals were diagnosed with RLS based on cTCD (Table 3), and they received treatment with the AMPLATZER PFO closure device. The study included 210 randomly assigned participants to either the occlusion group (n = 117) or the sham surgery group (n = 93). The primary endpoint of reducing migraine attacks by at least 50% has not been achieved. However, in secondary endpoints, the occlusion

**Table 3.** Right-to-Left Shunt Grading Criteria[5]

| | RLS magnitude | cTTE/cTEE | cTCD |
|---|---|---|---|
| Grade 0 | No RLS | No microbubbles in the left heart cavity. | No microemboli signal in cranial circulation |
| Grade I | Little RLS | <10 microvesicles/frame in the left heart cavity | 1-20 microbubble signals (1-10 unilaterally) |
| Grade II | Medium RLS | 10-30 microbubbles/frame in the left heart cavity | >20 microbubble signals (>10 unilaterally), non-curtain-like |
| Grade III | Large amount of RLS | Left heart >30 microbubbles/frame or left heart almost full of bubbles, cloudy chambers | Emboli signal is curtain or shower-like |

The table illustrates the grading criteria for right-to-left shunt (RLS) using contrast transthoracic echocardiography (cTTE), contrast transesophageal echocardiography (cTEE), and contrast transcranial Doppler sonography (cTCD).

group experienced more migraine days per month (3.4 vs. 2.0, $P = .025$) and had a higher rate of complete migraine remission (8.55% vs. 0.97%, $P = .010$). Six patients (2.9%) experienced self-limiting surgery-related adverse events, and 1 (0.5%) had a non-sustained atrial fibrillation-related adverse event during the procedure.[30]

Recent research has demonstrated that atrial fibrillation significantly increases the likelihood of adverse clinical outcomes, including heart failure, acute myocardial infarction, and major adverse cardiovascular events. Patients with atrial fibrillation are less likely to receive evidence-based therapies and are more likely to experience in-hospital complications such as heart failure.[31] Obstructive sleep apnea is consistently linked to the development of atrial fibrillation, which is a serious health concern because it is associated with significant morbidity and mortality. Postoperative atrial fibrillation complicates approximately one-third of all cardiac surgery cases, leading to major adverse consequences such as prolonged in-hospital stays, increased healthcare costs, and higher rehospitalization rates. The complications associated with atrial fibrillation are numerous and severe, including the formation of emboli, heart failure, early mortality, thromboembolism, hemodynamic compromise, arrhythmogenesis, and stroke. Atrial fibrillation is associated with a greater cost, extended hospital stays, and a higher incidence of cardiac and respiratory complications. Additionally, it is associated with an increased risk of bleeding complications, which is 5.5 times greater. This condition also independently predicts postoperative complications, including death, and a significant reduction in long-term survival.[32] The results of this study align with those of previous studies that reported higher in-hospital and long-term mortality rates among patients with atrial fibrillation. The grading criteria for the ((RLS) are presented in Table 3. The language used was strictly American English, with adherence to spelling, specific terms, and phrases (Table 3).

Although none of the 3 studies achieved their primary treatment endpoints, the secondary endpoints in the last 2 studies suggested that PFO closure could effectively improve the clinical symptoms in patients with migraine. In 2021, Mojadidi et al comprehensively analyzed the original data from PRIMA and PREMIUM clinical trials. They redefined the endpoint and studied 337 subjects, with 176 randomized to the PFO closure group and 161 to the medical treatment group. After 12 months of follow-up, the analysis yielded results on 3 out of the 4 efficacy endpoints: a significant reduction in the average number of monthly migraine attacks (3.1 vs. 1.9, $P = .02$), a notable decrease in the monthly migraine attack count (2.0 vs. 1.4, $P = .01$), and a greater number of participants experiencing complete relief from migraines [14 (9%) vs. 1 (0.7%), $P < .001$]. The analysis showed that PFO closure significantly reduced the number of monthly migraine attacks and provided complete relief to some participants.[33]

The differences in the outcomes of these clinical trials may be attributed to the following: (1) bias in the selection of patients included in clinical trials is large, resulting in the omission of some migraine patients who might benefit; (2) for endpoint events, the standards for the formulation of various studies were not uniform; (3) some clinical trials lacked the evaluation of residual shunt after transcatheter PFO closure; (4) some trials could not rule out the interference of combined antiplatelet agglutination drugs on the test results, and the placebo effect of surgery could not be ruled out in non-double-blind trials; and (5) diverse and complex factors affecting migraine attacks were missed in these studies.

In recent studies, it has been challenging to establish the effectiveness of PFO closure in migraine patients. In 2021, the European Association of Percutaneous Cardiovascular Intervention, in collaboration with 8 European scientific societies and several international experts in related fields, screened the literature, conducted a systematic evaluation, and issued a multidisciplinary statement on the management of PFO. They recommended that conventional treatment for migraines could be used for PFO combined with migraine. However, they suggested that transcatheter PFO closure should only be used in clinical studies or as a complementary treatment method for MA and not as a conventional treatment strategy.[24]

There has been much debate regarding whether to close a PFO in individuals who have experienced a stroke or transient ischemic attack (TIA). Although evidence suggests that PFO closure is associated with a lower incidence of stroke and TIA, there is often a lack of focus on the critical aspect of long-term follow-up and the assessment of recurrent stroke or TIA after the procedure. The absence

of comprehensive data on post-procedure recurrent events represents a significant gap in the discussion and is essential for understanding the overall effectiveness and safety of PFO closure in preventing recurrent stroke or TIA in this patient population. Long-term follow-up data are necessary to assess the safety and efficacy of the procedure in preventing recurrent stroke and TIA, which would provide a more comprehensive understanding of the benefits and risks associated with PFO closure. This would guide clinical decision-making and improve patient outcomes.[34] In conclusion, discussions regarding PFO closure should include comprehensive long-term follow-up data to understand better the benefits and risks associated with the procedure. This information can aid in guiding clinical decision-making and enhancing patient outcomes. It is essential to maintain the original meaning of a sentence while ensuring that the language used is clear and precise. The use of American English should be strictly adhered to, including its spelling and specific terms and phrases.

It is important to recognize the transient and lasting effects of PFO closure, as they can increase the likelihood of new-onset atrial fibrillation/flutter. Although PFO closure may lower the probability of recurrent stroke/TIA, it is also associated with a greater risk of new-onset atrial fibrillation/flutter. In addition, early randomized controlled trials failed to show a significant reduction in the risk of recurrent stroke among patients undergoing PFO closure. Furthermore, there is no compelling evidence suggesting that the excess stroke risk in patients with migraine is exclusively attributed to PFO through paradoxical embolism. Although PFO closure substantially reduces the risk of recurrent ischemic stroke, it may occur in some individuals. Therefore, it is crucial to consider potential side effects of PFO closure when making clinical decisions.

## CONCLUSION

In summary, migraine and PFO have a high comorbidity rate; however, experts have different opinions on whether PFO induces migraine and further discussion is needed. To ascertain whether transcatheter PFO closure might be advantageous for patients with migraines, it is essential to delve deeper into the pathogenesis of both conditions and to establish more precise clinical trial performance criteria. Although medical therapy is currently the preferred approach for managing PFO and migraines, further investigation is needed to establish a clearer understanding of the potential benefits of transcatheter PFO closure in patients with migraine. Migraine represents a significant global public health challenge, resulting in substantial personal and societal burden. It is expected that future multicenter, large-scale, prospective, double-blind, randomized, controlled clinical trials will provide further insights into the potential impact and long-term effectiveness of transcatheter PFO closure in alleviating migraine. These studies can serve as a foundation for making clinically sound decisions regarding when to recommend transcatheter PFO closure, ultimately offering relief to people living with migraine, enhancing their quality of life, and reducing the societal burden associated with this condition.

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