Yemen Journal of Medicine

https://yemenjmed.com

Article information

DOI: 10.63475/yjm.v4i2.0190

Article history:
Received: 09 August 2025
Accepted: 27 August 2025
Published: 22 September 2025

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How to cite this article
Habas E, Habas A, Alarbi K, Habas E, Baghi M, Habas A, et al. Pathophysiological insights and clinical implications of patent foramen ovale-related stroke: a comprehensive review. Yemen J Med.2025;4(2):277-293

Review Article

Pathophysiological Insights and Clinical Implications of Patent Foramen Ovale-Related Stroke: A Comprehensive Review

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ABSTRACT

Patent foramen ovale (PFO) is a prevalent congenital cardiac anomaly. It is increasingly acknowledged as a significant factor in cryptogenic ischemic stroke, especially among young adults experiencing otherwise unexplained cerebrovascular incidents. This review summarizes recent advances in the epidemiology, pathophysiology, diagnostic strategies, and management of PFO-related stroke. The article examines the intricate mechanisms of PFO-associated strokes, including paradoxical embolism, in situ thrombus formation, and atrial cardiopathy, while emphasizing the significance of anatomical risk factors like large shunt size and atrial septal aneurysm. The clinical implications of PFO in various disorders, such as migraine with aura, decompression sickness, and high-altitude pulmonary edema, are also analyzed. Diagnostic modalities such as echocardiography and transcranial Doppler are compared, focusing on their sensitivities and procedural details. The review focuses on evidence-based methods for medical, interventional, and device-based closure of PFO, highlighting patient selection and ongoing controversies. The ongoing uncertainties surrounding causal relationships, risk stratification, and optimal therapy highlight the necessity for continued research. This review offers a current synthesis for clinicians and researchers addressing the challenges associated with the evaluation and management of PFO in stroke prevention. To achieve the aims of the article and make it concise, PubMed, Google, EMBASE, Google Scholar, and Scopus were searched for original and review articles published in the last 10 years. Several keywords, phrases, and texts were utilized.

Key words: Patent foramen ovale, cryptogenic stroke, paradoxical embolism, right-to-left shunt, PFO closure, stroke prevention

INTRODUCTION

A stroke is defined as an abruption of cerebral blood flow of ischemic vascular cause resulting in a focal neurological deficit. On the other hand, a transient ischemic attack (TIA) is a brief episode of symptoms similar to those of a stroke, which results from a temporary obstruction of cerebral blood flow. TIA often lasts just a few minutes and does not result in lasting neurological deficits. Ischemic stroke (IS) is a syndrome resulting from cerebrovascular events that induce brain infarction. IS is due to local or systemic causes.

Young patients experiencing IS do not often present with conventional cerebrovascular risk factors. About 16.7% of strokes occur in the population aged <60 years, with 30% classified as cryptogenic. [1] Paradoxical embolism via a right-to-left cardiac shunt, including patent foramen ovale (PFO), atrial septum aneurysm (ASA), or a combination of PFO and ASA, can lead to cryptogenic brain IS. Transthoracic echocardiography, transesophageal echocardiography (TEE), and cardiac magnetic resonance imaging can effectively visualize PFO, ASA, and the morphological characteristics of PFO, which are crucial for comprehending the interplay of these pathological factors that contribute to IS. [2,3]

PFO is an interatrial communication that fails to close after birth and has been found more frequently in people who have an IS of uncertain cause (cryptogenic stroke [CS]). [2] PFO is well documented to predispose and increase the paradoxical right-to-left embolization. The right-sided heart has been identified as a potential source of embolic brain insult, either due to heart-originated or venous embolism in the existence of right-to-left heart shunt (RLS), which causes bypass of the pulmonary embolus filtering function. [1] Clots migrate from the systemic venous circulation into the systemic arterial circulation. It was reported that a venous clot that is >6 mm has a 50% chance of traveling to the left side of the heart. [4]

PFO and atrial septal abnormalities are the two most common shunts between the atria. Up to 25% of the population has a PFO of varying size, with a higher prevalence in patients <55 years with CS. It was believed that PFO is a disease; however, it is currently considered a remnant of normal fetal circulation that fails to close completely after birth. On several occasions, the PFO contributes to embolus shunting to cause cerebral IS, known as PFO-attributable cerebral emboli. [5] While PFO remains the most common type of cardiac abnormality, the majority of the affected individuals remain asymptomatic throughout their lifetime. Furthermore, PFO leads to cardiac structure abnormalities and cardiac arrhythmias such as atrial flutter, atrial fibrillation (AF), and supraventricular tachycardia, precipitating IS. [6]

This review article will provide an update on the epidemiology, pathophysiology, management, novel medicines, debates, discrepancies, and a critical evaluation of existing hypotheses and evidence regarding PFO and its association with IS, as well as prospects. The objectives have been accomplished by doing research on PubMed, EMBASE, Google Scholar, Google, and Scopus for publications published from January 2015 to May 2025. Various terms and keywords, including PFO, IS, stroke in young individuals, right-to-left shunting, congenital cardiac shunts, and paradoxical embolism, were utilized.

EPIDEMIOLOGY AND CLINICAL IMPLICATIONS OF PFO AND STROKE RISK

PFO occurs in 27% to 34% of the general population. [6,7] It is characterized by a persistent interatrial communication, which is the most prevalent cause of right-to-left shunt. The majority of PFOs are clinically silent; however, their prevalence rises to 29% to 73% in younger patients (<55 years) experiencing CS, indicating a potential pathophysiological role in paradoxical embolism.

Stroke epidemiology indicates significant patterns pertinent to PFO pathology. Stroke impacts 17 million individuals worldwide each year, occurring at a rate of one event every two seconds, with 5% to 10% of cases in adults under 50 years of age. [8] It is noteworthy that 40% of ISs in younger patients (<50 years) are classified as cryptogenic despite comprehensive investigation, [9,10] and the prevalence of PFO in this demographic significantly surpasses population averages. [11] Meta-analyses involving 3,364 patients from 23 studies indicate a prevalence of PFO ranging from 12% to 78% in cases of CS, compared to 6% to 33% in control groups with identified stroke etiologies. [11] The strongest associations are observed in younger populations, showing a 3- to 6-fold increased risk. [1,6]

The clinical significance of PFO is contentious, influenced by various factors such as its high prevalence in the population, with 25% of PFOs identified as incidental. There is an association with CS in younger patients, and the potential for paradoxical embolism presents a credible mechanism. Nonetheless, some instances may merely reflect incidental coexistence.

Demographic factors further complicate risk assessment. The incidence of stroke exhibits significant racial disparities, being twofold higher in African Americans, and demonstrates geographic variation, with an increasing burden observed in low- and middle-income countries. Pediatric stroke, though infrequent (1:4,000 neonates, 1:2,000 children), [12] exhibits unique etiologies such as congenital heart disease and sickle cell anemia, [12] with potential contributions from PFO-associated mechanisms.

Current evidence indicates that PFO is a significant modifiable risk factor for CS in specific populations, especially among younger patients lacking alternative etiologies. [6,11] Nonetheless, the population-attributable risk remains a topic of debate due to its high prevalence and frequent incidental detection, [13,14] highlighting the necessity for meticulous patient selection when evaluating intervention options.

PATHOPHYSIOLOGICAL MECHANISMS OF STROKE ASSOCIATED WITH PFO

Since Cohnheim's 1877 report, the PFO has been implicated in paradoxical embolism due to its role as a remnant of interatrial communication. [1] This underpins antithrombotic and device closure therapies. Alternative mechanisms include in situ PFO thrombus formation, atrial arrhythmias, or left atrial dysfunction. [2] Observational cohorts associate smaller shunts with higher stroke risk than larger ones, though RCT control arm data show the reverse or neutral effects. [3] This inconsistency may reflect measurement error, patient

heterogeneity, participants' characteristics, or suggest alternative pathophysiological pathways.

The embryological origins of the PFO elucidate its varying clinical significance. In fetal development, the foramen ovale facilitates right-to-left shunting of oxygenated blood, with postnatal closure occurring in 80% to 90% of individuals due to the fusion of the septum primum and secundum. [15] Failure of this closure results in residual communication, which may serve as a potential pathway for thromboembolism; however, only a subset of PFOs is clinically significant. [13,14]

PFO-associated IS typically arises from paradoxical embolism, wherein venous thrombi circumvent pulmonary filtration through a right-to-left shunt, resulting in cerebral artery occlusion. [1] The principal processes of thrombus development in PFO patients encompass paradoxical embolism, in situ thrombus formation, atrial cardiopathy, and hemodynamic anomalies. Furthermore, various anatomical and hemodynamic abnormalities precipitate thromboembolism.

PARADOXICAL EMBOLISM

Venous thromboembolism (usually 1–4 mm) originating from the deep veins of the lower extremities or pelvic veins passes through the PFO when right atrial pressure surpasses left atrial pressure (e.g., during Valsalva maneuver [VM] or inspiration). [5,6] The anatomical configuration of the aortic arch predisposes smaller emboli (1–2 mm) to preferentially enter the carotid or vertebral arteries due to their elevated location. In contrast, larger emboli become lodged in larger vessels. [6,16]

In-Situ Thrombus Development

Recent data indicate that endothelial dysfunction in PFO tunnels facilitates the formation of local microthrombi, especially in individuals with CS. [17] Simultaneously, intracardiac optical coherence tomography (OCT) identifies thrombi and endothelial abnormalities in PFOs of stroke patients, which are not seen in controls. [18] In 2021, intracardiac OCT revealed microthrombi in 11/11 stroke patients with PFOs and endocardial irregularities in 9/11, while 7 stroke-free controls had no abnormalities. [18] These findings do not clarify thrombus origin (in situ vs. trapped emboli) but may help distinguish pathogenic from incidental PFOs. Another 2021 study proposed that PFO closure reduces intracardiac/venous homocysteine (linked to thrombophilia), suggesting PFOs may tilt the coagulation cascade toward thrombogenesis. [19] Further research is needed on PFO diameter and embolic shunting rates.

ATRIAL CARDIOPATHY AND HEMODYNAMIC VARIABLES

A PFO can cause atrial dysfunction, resulting in arrhythmias and blood stasis, hence elevating the risk of thrombosis independently of AF. [20,21]

Atrial cardiomyopathy can be the site for arrhythmia and thrombogenesis. AF is rare in medically managed PFO patients, making atrial arrhythmia an unlikely stroke mechanism. [15,20] However, PFO-associated atrial cardiopathy may contribute to thrombogenesis, albeit less prominently than in large atrial septal defects (ASDs). [20,21] The ARCADIA trial (Apixaban to Prevent Recurrence After Cryptogenic Stroke in Patients With Atrial Cardiopathy) is testing whether anticoagulation outperforms antiplatelets in CS with atrial cardiopathy; PFO patients are a key subgroup. [22] The trial's results reported that apixaban was not superior to aspirin for decreasing the attacks of recurrent strokes in the studied participants.

ANATOMICAL AND HEMODYNAMIC MECHANISMS

Atrial Septal Aneurysm (ASA)

ASA is characterized by a septal excursion over 10 mm, which enhances the mobility of PFO and increases the volume of RLS. [23] The frequency of ASA in adults is 2.4%. It is linked to mitral regurgitation (39%) and arrhythmias (16%). [24] All these factors increase thromboembolic genesis and stroke. TEE detects ASAs more effectively than transthoracic echocardiography (TTE), which may overlook 47% of ASAs due to their dynamic characteristics. [25]

Shunt Dimensions and High-Risk Characteristics

Observational studies indicate a correlation between large PFOs (>4 mm) and ASA with stroke; however, randomized controlled trial data present contradictory findings. [26] Moreover, the Eustachian valve or Chiari network may channel venous flow towards the PFO, hence promoting embolism. [6]

Emboli originating from deep vein thrombosis exhibit a predilection for occluding specific sites in the brain; for instance, emboli of 3 to 4 mm in size can obstruct cerebral arteries as narrow as 1.9 mm. [5,6] Left-hemisphere strokes are reported more commonly (56%) than right-hemisphere occurrences (44%), possibly due to clinical detection bias (aphasia vs. neglect). [27–29] Notwithstanding these breakthroughs in the potential pathways of stroke in POF, several controversies and unresolved questions remain. Certain studies suggest a correlation between tiny PFOs and others with big shunts, [26] prompting the inquiry into the significance of PFO size in assessing IS risk. The other contentious issue is whether the ASA constitutes a distinct pathologic lesion. The current ARCADIA study may elucidate whether anticoagulation is advantageous for PFO patients with atrial cardiomyopathy and dysfunction. [30]

Clinically, Large shunt, ASA, and hypercoagulability are valid reasons for closing the PFO in cases of CS. [42,43] Conducting a workup to test for deep vein thrombosis, hypercoagulable conditions, and anatomical abnormalities (such as the Eustachian valve) is crucial to avert IS in patients with PFO. [6]

PFO-associated stroke has a complex pathogenesis, including paradoxical embolism, in situ thrombosis, and atrial dysfunction. Although high-risk anatomical characteristics (ASA, big shunt) may elevate the probability of stroke, their predictive significance necessitates additional enhancement. Future studies must elucidate the thrombogenic pathways specific to PFO to enhance patient selection of management strategies for RLS of blood and emboli. **Table 1** summarizes the pathophysiology mechanism of the thromboembolic features of stroke in PFO.

Table 1: Pathophysiology mechanism of the thromboembolic features of stroke in PFO.

Mechanism	Description	Key features	Diagnostic tools	Clinical significance
Paradoxical embolism	Venous thrombi cross PFO	R-L Shunt	TEE, Bubble Echo	Typical of PFO stroke
In-situ thrombus	Local microthrombi form in the PFO	Endothelial Abn	OCT, TEE	Pathogenic potential
Atrial cardiopathy	Atrial dysfunction, arrhythmias	AF is rare, stasis	EKG, MRI, Biomarkers	Minor role in PFO stroke
Anatomical features	ASA, Shunt size, Eustachian valve	ASA >10mm	TEE, TTE	May increase stroke risk

PFO: patent foramen ovale; ASA: atrial septal aneurysm; TEE: transesophageal echography; TTE: transthorax echocardiography; CS: cryptogenic stroke; MRI: magnetic resonance image; R-L shunt: right-to-left shunt; OCT: optical coherence tomography.

COMMON COMPLICATIONS AND PRESENTATION OF PFO

Pulmonary Embolism (PE)

Venous thromboembolism exhibits preferential streaming. The usual normal path for venous blood flow is to the right side of the heart, lungs, left side of the heart, and then systemic arterial circulation. Through this pathway, the clots are directed towards the pulmonary vasculature, where they are trapped. Nevertheless, in the case of RLS as PFO, the emboli could travel to systemic circulation. It is documented that smaller clots (approximately 1–2 mm) tend to favor the cranial circulation.

The existence of the PFO was identified as an autonomous factor contributing to increased death among patients suffering from severe PE. [31] Patients with PFO exhibited a significantly higher mortality rate ($P = 0.015$), 33% versus 14% for those without PFO. This elevated mortality is thought to be a result of a higher incidence of IS and systemic embolization. [32] However, a study of 150 patients, of whom 37 patients had PFO and idiopathic pulmonary arterial hypertension. Although these patients had an increased prevalence of severe hypoxemia, long-term survival was not affected. Conversely, a cohort of 11,287 acute IS cases from the Canadian Stroke Network, only 89 individuals (0.78%) were diagnosed with PE during days 2 to 30 following their stroke presentation. The presence of PE was independently linked to an extended in-hospital stay (36 days) versus (16 days; $P = 0.001$). Furthermore, the death risk at 30 days was 25.8% versus 13.6% ($P < 0.001$), and a higher incidence of persistent disability was 85.4% versus 63.6% ($P < 0.001$). [33] The data may indicate the coexistence of embolic events across various vascular beds due to an elevated thrombotic burden, or it may reflect heightened rates of deep venous thrombosis following a period of bed rest during stroke recovery. Physicians must recognize these relationships and the increased morbidity and mortality associated with their occurrence.

The pathophysiology behind the increased risk of paradoxical venous emboli in PE is possibly that PE causes a transient rise of pulmonary arterial pressure (PAP) that might force the blood flow from right to left in PFO patients. However, further investigative projects are required to prove this theory.

High-Altitude Pulmonary Edema (HAPE)

Nearly 1% of climbers get HAPE during fast ascent, generally over 2,500 m. High-altitude rapid climbing raises PAP. [34] Mechanisms of HAPE include impaired transepithelial sodium transport, [35] leading to a fast increase in PAP [36,37] in response to high-altitude pulmonary alveolar hypoxia and hypoventilation. [37,38] However, a newer document claimed that there was no Cl-transport difference, and low nasal ion transport in HAPE climbers with increased reactive pulmonary vasoconstriction are not at risk of developing HAPE when they have sufficient ability to reabsorb the alveolar fluid, even in increased PAP status. [39]

Hypoxic hypoxia at high altitudes only increases PAP, not right atrium pressure, left ventricle pressure, systemic blood pressure, pulmonary capillary wedge pressure, and cardiac output. Experiments mimicking the ascent of Mount Everest showed marked ventilation-perfusion mismatch, lack of reversibility with 100% oxygen, and calculated shunt of 10% increasing up to 50% with exercise, likely due to intrapulmonary shunting. [40] A study showed sustained RLS through PFO at 4,200 m in a climber with HAPE that was absent at sea level and produced exclusively by cough and VM. [41]

Additionally, HAPE-susceptible climbers had greater PFO and poorer bubble shunting at high altitude than at sea level. [42,43] High-altitude low oxygen tension may increase PAP from PFO-induced RLS and reactive vasoconstriction. Shunting causes reduced mixed venous saturation and systemic desaturation, which may elevate PAP and cause hypoxia-induced pulmonary edema. [6] HAPE risk factors include impaired ventilatory adaptation at high altitude and RLS via PFO. [43,44] Hence, high-altitude climbers have a higher PFO risk and arterial thrombosis that might lead to thrombotic stroke. To prove or disprove this assumption, new research projects are required.

Migraine

Migraine headaches are recurring, paroxysmal disturbances that cause pulsatile or throbbing headaches lasting 4 to 72 hours. Migraines may include nausea, vomiting, and light or sound sensitivity. There are two main types of migraine headache: aura and non-aura. Before or during a headache, an aura is a brief neurological sign related to modulatory function. Visual (scintillating scotoma), sensory (numbness of the hand), dysphasic (atypical speech), or motor modulatory auras exist.

One in eight people has migraines. Nearly 33% of migraineurs have neurological "aura" before the headache. Although migraine and PFO are common in the general population,

migraine with aura is substantially related to PFO (41%–89%) compared to migraine without aura (7%–34%) or aura with no migraine (20%–25%). [45] Transcranial Doppler (TCD) RLS flow decreases from aura-associated migraine to migraine without aura, indicating a "dose response" phenomenon. [46] Hemorrhagic telangiectasia and cyanotic cardiac disease. [47,48] Both circumstances associated with severe RLS enhance migraine headache frequency, confirming the idea that arterial venous blood flow increases headache and migraine frequency. Due to paradoxical embolization of micro-bubbles or foam particles, agitated saline echocardiography (bubble study) or TCD examination [49] and venous insufficiency sclerotherapy [49] may cause migraine. [6]

Another argument is that pulmonary circulation disintegrates vasoactive chemicals in venous blood, avoiding migraine. Platelets emit serotonin, a neurotransmitter, into the pulmonary circulation. [50,51] Serotonin and other vasoactive chemicals escape the pulmonary deactivation site action in RLS, causing cerebral buildup and migraine. Of 117 individuals without cardiovascular risk factors, 43 suffered stroke/TIA, 49 experienced migraine, and 25 were asymptomatic. Only migraine and stroke patients had PFO tunnel microthrombi and defective endothelium on OCT. [17] Other case reports imply the PFO may cause thrombus. [52] The importance of such observations is uncertain. IS is connected to migraines with aura in many studies. Morning migraine with aura is common in PFO-associated stroke. [53,54] Evidence shows migraine and aura are separate cardiovascular risk factors. [55] Vasomotor reactivity problems may also unify RLS. [56]

In some others, transcatheter RLS correction decreases migraine symptoms, [57] but not the aura, indicating there may be another biological cause. [50] PFO closure eliminated migraines, reduced migraine events, and reduced migraine days per month in 337 subjects (176 randomized to PFO closure) using individual patient data from PRIMA and PREMIUM. Interestingly, migraineurs with frequent aura (>50%) benefited most. After transcatheter ASD closure, some patients have more migraines than after PFO closure. [58] However, adding clopidogrel to aspirin reduces migraine incidence for three months. In patients with a large PFO shunt, micro-bubble injection generated transitory cerebral hypoxia/ischemia, causing bioelectrical disturbance and headache symptoms in some instances. [59] TCD showed a similar degree of RLS, but no cerebral bioelectrical changes were identified in migraine-free patients, suggesting that brain hypersensitivity is essential to cause migraine headache. Platelet activation and vasoactive material may cause migraine with aura, since platelet P2Y12 inhibitors (clopidogrel and prasugrel in nonresponders) reduced migraine headache symptoms following PFO closure. Clopidogrel and prasugrel response enriches the RELIEF Migraine Study, which will randomize migraineurs to the Gore Septal Occluder Device. Understanding the PFO-migraine relationship may require a systematic study.

PFO-mediated RLS is linked to migraine inferentially, although consistent data are lacking. Migraines result from cerebral hypoxia. [64] Patients usually get their first migraine in their 20s, and strangely, migraine frequency and duration decrease with age, [65] independent of PFO patency. Thus, further investigation is required. Published data support: (A) In certain migraineurs, PFO frequency may cause migraine. (B) RLS shunted blood content may cause migraine. (C) The intrinsic brain mechanism(s) that generate CSD are unclear, yet PFO-related migraine triggering requires them. (D) PFO closure had variable effects on migraine frequency and intensity, indicating we know little about PFO-related migraine pathophysiology and how to select migraineurs who may benefit. To understand PFO migration pathophysiology, well-organized investigations are essential.

Atrial Arrhythmias in PFO

Atria structural abnormality or enlargement increases the rate of atrial arrhythmia, such as atrial flutter and AF. [60] AF should be ruled out in stroke/TIA patients with PFOs. Compared to 24 to 48 hours, longer Holter monitoring has shown a higher incidence of AF in stroke patients and PFO detection, suggesting a tailored strategy based on age and cardiovascular risk factors. [61] Studies have shown almost a 5-fold greater risk for AF and flutter after PFO closure compared to medical treatment alone. [62,63] The first 3 months after device closure show the most arrhythmic burden, [64] but it does not seem to affect recurrent stroke risk. It is uncertain whether AF noticed post-PFO closure could be due to covert pre-procedure paroxysmal AF not discovered during pre-procedure assessment, procedure-related atrial or pulmonary vein irritation, or device-related localized inflammation and conduction pathway damage. [6]

Furthermore, coexisting atrial myopathy, [65] release of nickel from the device until endothelization completes (interestingly, increased plasma nickel levels post-device deployment normalize within 3 months of the procedure), [66] increasing patient age, and the fact that PFO closure is merely a bystander or a variable combination of these factors. To date, no research has examined this patient group using sustained rhythm monitoring pre- and post-closure to clarify. Hence, research projects are required to investigate these issues.

Decompression Sickness

Decompression sickness happens when high-pressure inhaled nitrogen during diving dissolves in tissues or blood, forming gas bubbles upon ascent, mechanically impacting tissues or obstructing blood flow if a patient has a foramen ovale (PFO). [67] This status can facilitate the embolization of venous nitrogen bubbles into the arterial system. Nitrogen bubbles in the venous circulation during fast ascent induce decompression sickness, although life-threatening consequences are uncommon with adequate diving methods. [68] In the context of PFO, RLS may cause systemic embolization of gas bubbles, causing neurological, cutaneous, or cardio-respiratory symptoms that may lead to death. [68] Bubble creation peaks 30 to 60 minutes after diving, [69] but divers are frequently returning to the surface, stepping onto the boat, or hauling heavy diving equipment by then. All these activities include physical effort and a VM, which may reverse the right-left atrium pressure gradient.

In simulated dive studies, 47 divers with a PFO or post-PFO closure formed venous bubbles uniformly, but only those with unrepaired PFOs formed arterial bubbles. [70] Others have shown that divers with PFOs and high-risk traits are more likely to develop decompression sickness than those without PFOs. [67] High-risk characteristics PFO requires ASA, intra-atrial sputum (IAS) hypermobility, >2 mm septum primum-limbus

separation, or RLS in the resting state. Hence, it is advisable that PFO closure in divers with "high-risk" PFOs may prevent decompression sickness, [71] and the recreational divers do not necessarily need to undergo PFO screening or device closure.

Acute Myocardial Infarction

Despite normal coronary arteries, coronary artery embolization may cause acute myocardial infarction. The systemic circulation (LA appendage, aortic or mitral valve [thrombus or infective endocarditis vegetation], and left ventricle) or paradoxical embolization via a PFO or pulmonary arteriovenous malformation may cause coronary emboli. A recent assessment of 1,776 consecutive acute myocardial infarction patients from 2001 to 2013 found that 2.9% were from assumed coronary embolization; however, 38/52 were from LA appendage clot owing to AF. [72]

Cryptogenic Stroke

The oval fossa typically develops after complete closure of the foramen ovale post-birth. Oval fossa is observed in >30% of individuals aged ≥50 years. Patency preserves the chance for short-cut RLS during a VM and intense cough. PFO represents the most common etiology of RLS in adults. It primarily consists of fossa ovalis type PFO, which is linked to its embryological origin, ostium secundum type PFO, and, less frequently, mixed type PFO. From a pathophysiological perspective, a PFO is more likely to facilitate the passage of circulating emboli into the arterial circulation, attributable to the increased prevalence of RLS-related IS. The rare ostium primum defect is typically due to a bidirectional, left-to-right shunt that leads to bidimensional blood shunting. [1] It was reported that PFO duration and the frequency of its complications correlate significantly with RLS intensity. Furthermore, the size of the RLS, the absolute echocardiographic bubble size, and cardiac comorbidities directly correlate to embolization risk. [73]

Paradoxical embolisms are trapped in the PFO-shunting blood. Although not commonly recognized or routinely examined, paradoxical embolization-related stroke/TIA patients can experience hypoxia during exercise ("provoked exercise desaturation"), especially when climbing stairs, which increases calf vein compression and inferior vena cava (IVC) venous return. This might indicate increased venous blood RLS, causing systemic desaturation and paradoxical embolization. [74] However, these conclusions require further proof and study. **Table 2** summarizes the common complications and presentation of PFO with R-L shunting.

OTHER CAUSES INCREASE THE RISK OF RIGHT-TO-LEFT BLOOD SHUNTING THROUGH PFO

Heart-Implanted Devices and Stroke in Patients With Foramen Ovale

In an intriguing review of 6,075 cardiac implantable electronic device patients, 364 had PFO. At a follow-up of 4.7 ± 3.1 years,

Table 2: Common patent foramen ovale complications and presentations.

Clinical feature	Description	Prevalence/association	Notes
Asymptomatic	Most PFO patients show no symptoms.	Common	Typically discovered incidentally on echocardiography.
Stroke/cryptogenic stroke	Passage of thrombus via PFO leading to embolic stroke.	PFO is present in ~50% of cryptogenic stroke cases	Risk correlates with shunt size, presence of ASA, and cardiac comorbidities.
Migraine	Migraine, especially with aura, is associated with PFO—possibly due to shunted vasoactive substances.	Migraine with aura: 41%–89% PFO; Migraine without aura: 7%–34% PFO	Frequency/severity increases with RLS; PFO closure may alleviate symptoms in select groups.
Atrial arrhythmias	Atrial flutter/fibrillation post-PFO closure; possibly device or age-related.	Post-closure AF incidence <5%	Risk peaks within weeks of closure; long-term impact generally low, but monitoring recommended.
Decompression sickness	Gas embolism from the venous to arterial side via PFO during diving leads to neurological/ cardiopulmonary events.	Risk increases in divers with PFO, especially "high-grade" shunt	Closure may be considered for divers with severe decompression sickness and high-risk PFO traits.
Acute myocardial infarction	Rare paradoxical embolism through PFO causes coronary artery occlusion.	Very rare, but a higher suspicion is needed in younger MI patients	PFO closure may help prevent recurrence in embolic MI without atherosclerosis.
Platypnea-orthodeoxia syndrome	Positional dyspnea and hypoxemia due to RLS through PFO; symptoms worsen while upright.	Uncommon	Often related to anatomical changes (e.g., ASA) or increased right atrial pressure.
High-altitude pulmonary edema	PFO may facilitate the passage of blood-borne mediators contributing to edema at altitude.	Uncommonly linked	Mechanism speculative; not a routine indication for PFO closure.

R-L shunt: right-to-left shunt; ASA: atrial septum aneurysm; MI: myocardial infarction; PFO: patient foramen ovale.

8.2% of patients with PFO developed stroke/TIA, compared to 2% of those without PFO. After controlling for age, sex, AF, prior stroke/TIA history, and antiplatelet/anticoagulant treatment, PFO was revealed to be independently related to stroke/TIA (P <0.0001). [75] PFO-associated central venous line paradoxical thromboembolism has also been reported. [76]

Ebstein Anomaly

Ebstein anomaly is a tricuspid valve malformation that causes the septal and posterior leaflets to not delaminate or separate from the right ventricular myocardium, the anterior leaflet to elongate, and the functional annulus to move toward the RV apex. [77] The highest apical displacement occurs at the septal level; thus, the tricuspid regurgitant jet preferentially flows towards the IAS and may pass through a PFO or ASD, a frequent cardiac abnormality in these individuals. [78] Tricuspid regurgitation increases with activity; hence, patients should be evaluated for exertional hypoxia. Closing PFO/ASD may reduce hypoxia in correctly chosen individuals after hemodynamic examination. [79]

Obstructive Sleep Apnea (OSA), Stroke, and Patent Foramina Ovale

Multiple short studies and case series indicate a linkage between OSA, PFO, and stroke. A variety of cardiovascular risk factors may directly cause strokes in OSA patients. However, OSA is an independent stroke risk factor, [80] even in AF patients. [81] Studies have shown that OSA may have a 60% stroke prevalence, compared to 4% in age-matched adults. [82] OSA was found in 697 (68%) of 1,022 sleep study subjects. In a median follow-up of 3.4 years, 3.2% of OSA patients had a stroke, compared to 0.6% without OSA. [80]

OSA patients have a higher PFO rate, which can induce chronic hypoxia, increasing blood pressure, cerebral hypoperfusion, altered cerebral autoregulation, endothelial dysfunction, prothrombotic and proinflammatory milieu induction, and increased AF. [83] In these individuals, PFO-associated RLS may worsen systemic desaturation and increase stroke risk. A study of 48 OSA patients and 24 healthy controls indicated that 69% had PFOs compared to 17% of healthy participants. More critically, OSA patients with PFO showed greater post-Valsalva desaturations despite equal resting systemic arterial saturations. [84] These data show that PFO-facilitated RLS causes or worsens OSA hypoxia. Muscular relaxation during sleep causes Valsalva equivalence, which momentarily raises RA pressure and facilitates RLS via the PFO. Systemic desaturation narrows the baseline-hypopnea/apnea threshold gap, further destabilizing ventilatory effort. [85] Given the strong link between OSA, PFO, and stroke, PFO closure's effects on OSA parameters and stroke risk must be further studied.

The impact of PFO closure on OSA severity has mostly been studied in case reports. [86] A hypothesis-generating research study examined 40 consecutive newly diagnosed OSA patients by TEE. More than a third (35%) of PFOs were closed, and OSA therapy was delayed for 3 months. Polysomnography showed substantial decreases in apnea-hypopnea index, oxygen desaturation index, systemic arterial blood pressure, and echocardiographic left ventricular diastolic dysfunction indicators after PFO closure. [87] A similar trial, "PFO closure for Obstructive Sleep Apnea (PCOSA-1)," is recruiting patients to assess the effects of PFO closure on OSA symptoms.

CLINICAL FEATURES OF PERSISTENT FORAMEN OVALE

Most PFO patients are asymptomatic. The PFO is thought to facilitate the passage of chemicals or thrombus, potentially leading to various clinical outcomes such as stroke, migraine, decompression sickness, dementia, platypnea-orthodeoxia syndrome, generalized headache, and HAPE.

DIAGNOSTIC APPROACHES

A prospective population-based study found that ≤4 mm identified high-risk PFOs for IS/TIA. Ventricular assist device (VASD) grading 3 resulted in a bigger cumulative revision rate (CRR) than TTE. PFO is a potential conduit of paradoxical embolism and causes CS. Diagnostic methods for PFO are crucial in the management of PFO-related IS. PFO is associated with CS, and transcranial color-coded duplex sonography is useful for precise examination and diagnosis of PFO compared to TTE. Among a dozen anatomical features influencing stroke risk, the central feature is the length of the tunnel, and two adjacent septal characteristics are thought to promote tunnel development. A simple scoring model that predicted the usefulness of PFO closure in patients with CS. [88] All these features needed to be examined before implementing therapy.

Transesophageal Versus TTE in Diagnosing PFO

TEE is more sensitive in detecting PFO than TTE. The TEE sensitivity is because the ultrasound beam for TEE is perpendicular to the atrial septum, making it easier to obtain a clearer view of the curtain-like veil on the probe. [89] In addition, because the image quality can be greatly enhanced, the TEE that can replace the surgical operation can display the subtlety of the atrial septum. TEE is especially useful for observing small and complex PFOs. Hypothetically, because of the contrast agent, the ultrasound wave of TEE with increased resolution can better display the contrast-containing air bubbles moving between and in the atria. If there is a PFO, the contrast agent can shuttle between the left and right atrium, so TEE is better than TTE in diagnosing PFO.

Multivariate analysis shows that the air contrast agent can affect the RLS grade between the heart and brain. The RLS grade of the visually monitored opacification (VMO) group is higher than that of the non-VMO group in the study. The conclusion is that the PFO with a larger channel makes it easier to increase the RLS grade with contrast agent, and VMO is one factor that affects the increase in RLS grade with contrast agent in PFO. In addition, the air contrast agent affects the RLS grade between the heart and the blood system. When the contrast agent is present, the RLS grade of the posterior-negative Doppler-acoustic signal (DAS) group is higher than that of the posterior-positive DAS group. [90,91] In addition, as TEE is a new investigatory and diagnostic tool for PFO, it is necessary to assess its diagnostic accuracy, sensitivity, and specificity in large studies.

Transcranial Doppler

TCD ultrasound detects microembolic signals (MES) with a higher sensitivity than other methods. Because of an

association between RLS and PFO, TCD with the analysis of MES is of great clinical importance. PFO is associated with CS, especially in young adults. TCD ultrasonography is commonly used as a screening tool before TEE to assess right-to-left cardiac shunts. Although the diagnostic approach is standardized, differences in interpretation might occur. Different maneuvers like Valsalva, reverse Trendelenburg, and cough have been published to quantify the VM in a standard way. Missing a standardized maneuver could lead to low-rate detection of PFOs ≥2 mm in diameter.

The standardization of the VM effect in TCD is a helpful approach to guarantee comparable and accurate results, thereby increasing the probability of finding the PFO diameter. When patient data from an unselected inpatient cohort of a tertiary care center were analyzed according to this standardized maneuver, the agreement in VM measurement during and between different operators was too low to provide evidence that it is feasible in the clinical setting. [92] The lack of tenderization may contribute significantly to diagnosis and connective tissue size. Therefore, large projects are required for assessing TCD abilities in PFO and CS.

Cardiac Magnetic Resonance

Cardiac MRI provides multiplanar imaging of the heart using magnetic resonance technology, without ionizing radiation or contrast agents. High spatial resolution can identify and describe PFOs as accurately as TEE, as well as evaluate thrombus and anatomical factors that TTE or TEE might not easily pick up. Cardiovascular magnetic resonance (CMR) action strategies use contrast-enhanced magnetic resonance visible flow technology and have good sensitivity and specificity for identifying ASA and PFO-related stroke.

The correlation between PFO and stroke was studied in plateau residents. Cardiac MR, which included cine sequence images, was performed using 3.0 T Skyra MRI in 80 patients. All cases were evaluated blindly by two radiologists with more than five years of experience in brain MRI image analysis. The location, number, and anterior/posterior circulation of ischemic lesions were evaluated. Matching results were recorded: (1) the full width of the dura mater visible on neck imaging, and (2) basioccipital/percutaneous line position in the neck.

Echocardiography is the main method to detect the relationship between PFO and stroke, but the diagnostic rate is low, especially in elderly patients. CMR was used as the validation method to compare the results of echocardiography with the "gold standard." CMR's sensitivity and predictive values were higher than TTE and TEE for evaluating PFO and PFO-related acute infarction. Four methodological research projects used CMR to evaluate 25 individuals suspected of having a PFO with a mean age of 48 ± 15 years and a distribution of the PFO-tunnels-septum transversum (PFO-TSs), tunnels inside a patent tunnel on the near side, and the tunnel isosceles triangle plane. With the results of CMR, surgical validation examinations were carried out, and the false positive rate, miss rate, and diagnostic accuracy of the CMR results were evaluated. The results showed that 9 of the 25 individuals had PFO-TSs. This CMR multi-taxi technique effectively uses compression and release shots to ensure complete coverage of the PFO-TS narrow near-side tunnels. [93]

Reliability of Patent Foramina Ovale Diagnosis as an Etiology for Stroke

Despite the strong observed relationship between PFO and stroke risk, proving a pathogenic association in an individual patient is challenging. The patient's history and brain imaging findings suggest that RLS may be a cause of cryptogenic IS [15,94]; cardiac anatomical features, including ASA, shunt size, and tunnel length, must be assessed. PFO may cause stroke during or after a VM, including hard sexual activity, lifting, straining at stool, coughing, sneezing, or vomiting, or sleep apnea. [95,96]

Large PFO size, persistent pulmonary hypertension, VM, and the Mueller maneuver may enhance the risk of venous thromboembolism passing via the interatrial shunt. [15] PFO complicity increases with lower extremities deep or superficial venous thrombosis or PE within 48 to 72 hours of stroke onset. [97,98] Immobility (e.g., extended travel, surgery, or illness), dehydration, venous hypercoagulability (e.g., protein C and S deficiencies, factor V Leiden mutation, or prothrombin gene mutation), anatomic causes of venous congestion (e.g., May-Thurner syndrome), or a history of venous thromboembolism should be investigated. [15] Finally, the absence of atherosclerotic risk factors, including hypertension, hyperlipidemia, diabetes, and smoking, raises the possibility of PFO diagnosis.

The Paradoxical Embolism (RoPE) index estimates a patient-specific PFO-attributable percentage, or the chance that a PFO is pathogenic. [97] Younger age, cortical stroke on neuroimaging, lack of diabetes, hypertension, smoking, and previous stroke or TIA determine the 10-point RoPE score. Increased scores indicate increased PFO prevalence and PFO-attributable proportion. Attributable fraction estimates ranged from 0% to 90%, with PFO prevalence rising from 23% in individuals with a RoPE score of 0 to 3 points to 73% in those with a RoPE score of 9 to 10 points. [97] Increasing RoPE scores reduces stroke recurrence risk. This suggests that individuals whose stroke is most likely attributable to the PFO have the lowest chance of recurrence; hence, the RoPE score cannot be used to determine whether closure is beneficial. Note that the RoPE score does not account for high-risk PFO anatomical or physiological traits and should be assessed alongside other metrics.

PFO is more likely an incidental finding in individuals aged <55 years with lower risk characteristics, but potentially pathogenic in older patients with high-risk anatomic features and no additional stroke risk factors. [11] A data meta-analysis of all randomized closure studies is determining which patients are at greatest risk and most likely to benefit from therapy. [99] This approach for pathogenic PFO identification and clinical decision-making may replace the RoPE score, helping in management strategy selection.

MANAGEMENT

After discussing the possible pathophysiological mechanisms and complications, this section will discuss the management strategies that are applied to improve the quality of life and prevent complications. Although stroke has dropped from the third to the fourth most common cause of mortality, it still amounts to 6.1 million deaths each year worldwide, making

it among the leading causes of mortality and the top cause of serious long-term disability. It is estimated that the cost of stroke management was over $38.6 billion in 2008, making it one of the most expensive illnesses. About one-quarter of the 150,000 strokes that occur annually in the UK are thought to be due to a PFO. Since in most centers, including the Norfolk & Norwich University Hospital, echocardiographic assessment is not routinely undertaken in all patients with suspected stroke, this can be the cause of the underestimate for PFO as a precipitating etiology. [100] Stroke patients have an increased prevalence of PFO compared to the general population. The PFO should be considered in the workup of strokes of unknown cause when the patient is <55 years old or has an otherwise unexplained cause of stroke. Broadly, the management of PFO can be achieved by medical, interventional, or surgical approaches.

MEDICAL MANAGEMENT

For patients with CS or TIA and a PFO, the medical approach is still currently in use. Meta-analyses of published randomized controlled trials revealed that anticoagulation is not effective and shows an increased safety risk compared to the antiplatelet drug. CS and PFO past meta-analyses did not demonstrate an overall significant treatment benefit for PFO closure. This may be due to the published data of CLOSURE I after the Network Meta-Analysis. However, PFO closure is performed in the actual treatment. This meta-analysis included all randomized controlled trials giving peer-reviewed comparisons of the PFO closure policy to the patient's medical therapy after the CS. Thus, through Network Meta-Analysis, the substantial gap in evidence of PFO closure compared to clinical treatment is examined. [101] The study concluded that stroke rates were reduced with percutaneously implanted device closure compared to medical treatment alone, with these rates influenced by hypertension, ASA, and successful closure. The newly released trial data did not alter the landscape of medical literature.

Role of Antiplatelet, Anticoagulation, and Antiarrhythmic Therapy

The study results did not support the efficacy of occlusive treatment, encompassing PFO closure or the application of a medical device alongside pharmacological therapy. The multilateral experiment controlled the pharmacological treatment involving acetylsalicylic acid, warfarin, clopidogrel, and medical care, which included diet, education, and risk factor minimization, with follow-up conducted on experimental groups. No benefit of occlusive treatment compared to pharmacological treatment in decreasing the risk of stroke or TIA recurrence was demonstrated. The trial's size renders these results competitive. [116]

Over 50% of arrhythmia episodes occurred during the perioperative period, potentially attributable to scar tissue formation four weeks post-device insertion into the defect. Studies indicate that occlusive methods demonstrate greater effectiveness than pharmacological treatment in patients with PFO experiencing cerebral ischemic events. The number may be reduced, as no events were considered, TIA, and there are variations in the analysis of initial versus cumulative events. The scoring employed in this study may have also influenced the outcomes, as it accommodates numerous risks associated with events. Pharmacological treatment demonstrated a protective effect, albeit with some variability, in other scores, decreasing the risk of events by nearly twofold. Relying solely on pharmacological treatment for secondary stroke prevention may be inadequate in high-risk scenarios, highlighting the need for surgical intervention and/or a comprehensive range of treatment options. Current experimental evidence does not establish a definitive causal link between PFO and stroke. The study's limitations include the selection of the experimental group following the initial verified occurrence of stroke, TIA, or cryptogenic TIA. Nonetheless, the events influencing PFO frequently occurred prior to the neuroimaging. This defect may result in the erroneous selection of patients with advanced atherosclerosis, some of whom also presented with a PFO niche, reducing the efficacy of the conclusion.

The medical therapeutic strategy is for the non-high-risk patients. AF and flutter are very rare and usually recover after surgical closure. [66] This strategy depends on using antiplatelets (aspirin, clopidogrel) or anticoagulants (warfarin, direct oral anticoagulants [DOACs]) in select cases to reduce the risk of thrombosis and thromboembolism. The available 2020 guidelines recommendations are AHA/ACC: Class I recommendation for PFO closure in CS with high-risk features, [102] whereas the ESC recommends selective closure after multidisciplinary evaluation. [103] Further research is required to explore the benefits of Bioabsorbable PFO occluders. [104] Biomarkers such as serum calcitonin gene-related peptide, [105] intracardiac total homocysteine, [19] endothelial activation, fibrinolysis, and on-treatment platelet reactivity. [106] The efficacy requires further evaluation.

Surgical Closure of PFO

PFO can be closed with surgery, but that is an invasive procedure carried out less and less frequently as better closure techniques have evolved. Currently, transcatheter PFO closure is the standard with implantation of a septal occluder device. This device is delivered to the interatrial septum through transfemoral venous access, in most cases under fluoroscopic and transesophageal echocardiographic guidance. The device consists of two self-expandable discs connected by a waist. The discs fix on the septal sides and the waist in the tunnel of the PFO. Surgical PFO closure involves an invasive procedure with higher complication rates than transcatheter PFO closure. Reported surgical techniques include direct suture or patches, and occasionally, PFO ligation. Surgical PFO closure nowadays is performed less frequently as transcatheter PFO closure has emerged as an alternative, effective method with lower periprocedural risks. [107]

PFO closure aims to block the passage of paradoxical emboli from the venous to the arterial circulation. After PFO closure, re-evaluation of the atrial septum with imaging investigations 6 months after the procedure is mandatory for verification of the correct implantation of the device and the detection or exclusion of any related anatomical complications. Afterwards, lifelong secondary prevention therapy as recommended by the stroke guidelines is mandatory. In addition, after PFO closure, an elective re-evaluation investigation is usually recommended every 2 to 5 years, largely depending on the patient-specific clinical findings. [108]

Interventional Therapy for PFO: Indications, Techniques, and Clinical Evidence

While often asymptomatic, PFO has been implicated in CS, paradoxical embolism, and migraine with aura. [109,110] Over the past decade, interventional PFO closure has emerged as a viable treatment option for select patients, supported by multiple randomized clinical trials (RCTs). In this review section, the indications, techniques, outcomes, and future directions of PFO closure will be discussed.

INDICATIONS FOR PFO CLOSURE

The strongest indication for PFO closure is secondary stroke prevention in patients with CS and high-risk PFO features, including large shunt size (≥30 microbubbles on TEE), ASA, prominent eustachian valve, or Chiari network. Three major RCTs—CLOSE (Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelet Therapy to Prevent Stroke Recurrence), REDUCE, and DEFENSE-PFO (Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale)—demonstrated that PFO closure reduces recurrent stroke risk by 50% to 77% compared to medical therapy alone. [111,112] Migraine with Aura in PFO is another indication for PFO closure. However, observational studies suggested PFO closure may improve refractory migraine, RCTs (PRIMA (Percutaneous Closure of PFO in Migraine with Aura), PREMIUM (Percutaneous Closure of Patent Foramen Ovale in Patients With Migraine)) showed no significant benefit. [113] Current guidelines do not recommend closure for migraine alone. [114] Other Potential Indications, such as decompression sickness in divers (limited evidence) [115] and platypnea-orthodeoxia syndrome. [116] Furthermore, certain anatomical features, such as a large PFO size, the presence of an ASA, a long tunnel, and associated structures like a prominent Eustachian valve, are considered high-risk morphologies that increase the likelihood of paradoxical embolism. These anatomical characteristics are important indications for surgical or percutaneous intervention, especially in patients with CS or other embolic events.

The interventional Techniques for PFO closure include device and medical therapy. Device closure is the gold standard technique. The procedure is conducted using Amplatzer™ PFO Occluder (Abbott) or Gore Cardioform™ Septal Occluder (WL Gore). The procedure can be conducted either under sedation or under general anesthesia. It is performed under TEE or intracardiac echocardiography guidance. A femoral venous access is used for catheterization to reach the right heart, and then the device is deployed across the PFO. The success rate of this technique is 95% with low complication rates. [117] The main complications of this procedure are periprocedural (1% to 3%), including device embolization, AF (5% to 10%), and vascular access complications. The long-term complication after 5 years is residual shunt (5% to 10%) and rarely device thrombosis.

CONTROVERSIES AND ONGOING RESEARCH

Experts are unsure of the correlation between PFO and stroke. Additionally, patients diagnosed with stroke with the concomitant occurrence of PFO are treated with anticoagulant therapy for various periods. In consequence, these patients often attend the hospital, AF being detected with increased frequency. The correlation of these two diseases has sparked many controversies and questions regarding how they should be managed now. [118]

PFO is a gap between the atria resulting from the closure of the fossa ovalis after birth. It is a common anatomical defect in an otherwise structurally normal heart. However, PFO has been associated with CS. One of the etiological mechanisms of IS is the paradoxical embolism from the circulatory source directly to the central nervous system, bypassing the pulmonary vascular bed. [1] The PFO-attributable embolic event does not effectively leave the brain circulation. Instead, it wanders with the blood current in the brain blood vessels and into the brain substance before finally escaping through vessels that connect the arterial and venous sides of the brain.

PFO is a highly prevalent cardiac structural abnormality in the general population, with a reported frequency ranging from 10% to 34%, depending on the diagnostic modality used. CSs, which constitute approximately 30% of all ISs, are generally defined as strokes attributed to an undetermined cause after extensive evaluation. There is conflicting data about whether PFO is the direct cause of a stroke, a risk factor for the development of stroke from other causes, or an incidental finding in patients with CS, given their high frequency in both stroke and control populations. The most promising potential stroke mechanisms in association with PFO are: (a) paradoxical embolism from a venous clot that traverses the PFO and leads to stroke; (b) in situ clot formation within the PFO; (c) atrial arrhythmias due to electrical signaling disruption along the interatrial septum with subsequent thromboembolism. [1] Synergistic action of the main known clinical and anatomic risk factors for stroke has been proposed, delineating a conceptual model where a young person with a large PFO and ASA would have a 5% risk of embolic events, multiplied by the presence of thrombophilia or high-intensity sports activity, and further multiplied by the presence of subclinical AF. The multicenter Risk of Paradoxical Embolism score has been developed to grade PFO-attributable stroke risk, and it has been validated with a prospective, multicenter, population-based case-control study. Over the last decade, many investigators have tried to correlate other PFO echocardiographic features with the risk of developing a stroke attributable to PFO. None of these attempts has provided straightforward results, as there are multiple contradictory findings in the available literature pool, and sometimes the proposed new factors can even be negatively associated with the risk of stroke. [119]

Current guidelines (AHA/ESC) rely on RCT data, recommending closure based on clinical risk factors (RoPE score, ASA) rather than shunt size alone. The controversy between the reported data can be due to selection Bias in observational studies, Differences in PFO assessment methods, heterogeneity in stroke mechanisms, temporal and Procedural factors, statistical power, endpoint definitions, and possibly publication bias. In summary, Observational studies suggest that large PFOs increase stroke risk due to methodological biases. At the same time, RCTs show no clear effect of PFO size because they control for confounders and focus on clinical outcomes.

RESEARCH GAPS AND FUTURE DIRECTIONS

The proportional contributions of paradoxical embolism, in-situ thrombosis, atrial cardiopathy, and structural factors

(ASA, shunt size) to stroke risk are unclear. The mechanisms that distinguish pathogenic from accidental PFOs are unclear. We know little about the cellular and molecular pathways that cause local microthrombus development in PFO tunnels. Prospective mechanistic investigations employing OCT, CMR, and tissue sampling to distinguish in situ thrombi from embolic events in PFO and stroke patients. Genetic/biomarker research to identify PFO patients at risk of endothelial dysfunction and thrombogenesis. These two studies must investigate pathogenesis and biomarkers.

No established approach uses anatomical characteristics, clinical variables, and biomarkers to distinguish incidental from pathogenic PFOs. Though beneficial, the RoPE score excludes anatomical high-risk characteristics and does not predict recurrence or closure benefit. Creation and validation of composite risk models using clinical, anatomical, and laboratory data, perhaps with AI-based image analysis and machine learning predictions. Prospective longitudinal cohort studies of PFO carriers correlate outcomes with anatomical characteristics, concomitant risk factors, and pharmacogenetics.

Unstandardized VM and bubble study criteria and methodology across TEE, TTE, and TCD. Small or complicated PFOs have unknown diagnostic sensitivity and specificity, especially in older individuals. Large multicenter studies comparing TEE, TTE, TCD, and CMR imagery with standardized procedures and outcome validation. More research is needed to determine the appropriate shunt size and tunnel length cut-offs for stroke risk.

Contradictory findings on stroke device closure, notably for elderly patients and those with non-cerebral symptoms, such as migraine and decompression sickness. Optimizing antithrombotic treatment (antiplatelet vs. anticoagulation) in atrial cardiopathy patients is uncertain. Randomized controlled studies in high-risk categories (e.g., older persons, migraineurs, divers) to determine who benefits from closure and with what device. More comparative studies of antithrombotic regimens post-closure, especially in patients with atrial dysfunction or arrhythmia.

RLS, vasoactive agents like serotonin, and brain hypersensitivity in PFO are unknown physiologic links. Intermittent migraine relief from closure continues. Migraineurs who may benefit from closure are unknown. Mechanisms of vasoactive chemicals, serotonin metabolism, and CSD pathways in PFO-related migraine. Patient enrichment studies (like the RELIEF trial) to find biochemical or imaging factors predicting migraine closure response.

Limited prospective evidence on whether PFO closure improves systemic hypoxia, sleep apnea, decompression disease, or altitude consequences. Randomized/interventional trials on cardiopulmonary non-stroke closure outcomes, including OSA parameter changes, decompression risk, and high-altitude adaptation.

Long-term evidence (>5 years) on device safety, late problems, arrhythmia risk, and biomaterial influence on heart tissue is scarce. Device registries and post-market monitoring studies documenting late complications, arrhythmia, and biomaterial impacts.

Lack of realistic clinical algorithms for patient selection that integrate all information and personalized suggestions. Delphi consensus guideline development with novel biomarkers, imaging characteristics, and clinical trial data.

In summary, mechanistic knowledge, diagnostic procedure standardization, management data (particularly for non-stroke indications), and actionable clinical algorithms are lacking. To improve PFO diagnosis, management, and results, future research should combine imaging, molecular biology, data analytics, and rigorous clinical trials.

The above-discussed controversies and perspectives for PFO-related stroke are summarized in **Table 3**.

Future research should prioritize the incorporation of novel biomarkers and sophisticated imaging techniques to differentiate pathogenic from accidental PFO instances more effectively. Research on biomarkers of endothelial dysfunction, circulating prothrombotic factors, and cardiac biomolecular profiles shows potential for enhancing risk stratification. Furthermore, the utilization of artificial intelligence and machine learning algorithms to integrate clinical, anatomical, and laboratory data may improve diagnostic precision and patient selection for PFO closure. Standardization of diagnostic methods, encompassing VMs and bubble investigations across imaging modalities, is essential to diminish variability. Extensive prospective cohort studies and randomized trials targeting various patient subgroups, such as elderly individuals, those with migraines, and divers, are crucial for elucidating indications and enhancing therapeutic strategies. The long-term safety of devices and the significance of tailored antithrombotic therapy necessitate more investigation to enhance outcomes.

CLINICAL SUMMARY

PFO as a Stroke Etiology in Specific Patients

CS in young persons (under 60 years): PFO occurs in almost 50% of cases compared to 25% in the normal population, indicating a potential pathogenic involvement. A significant shunt (>30 microbubbles on TEE), ASA, or Eustachian valve/Chiari network increases the risk of stroke. Paradoxical embolism is the principal cause; however, in-situ PFO thrombus and atrial cardiopathy may also play a role and should be ruled out.

Diagnosis: Essential Assessments for PFO Identification

TEE with bubble studies is the definitive standard, exhibiting superior sensitivity compared to TTE. TCD serves as an effective screening instrument for right-to-left shunt. Cardiac MRI can evaluate thrombus and anatomical risk factors, although it is less accessible.

Percutaneous Closure of PFO

PFO closure is indicated for patients under 60 years with CS and high-risk PFO characteristics (large shunt, ASA), as well as for those without other stroke etiologies (e.g., AF, major-artery atherosclerosis). Relative indications include elderly patients (>60 years) or those with poor RoPE scores, indicating accidental PFO. Furthermore, individuals have migraines with aura; nonetheless, closure is not commonly advised, since research demonstrates uneven efficacy.

Table 3: Controversies and future directions in PFO-related stroke.

Category	Current controversies and unresolved questions	Proposed future directions and research needs
Pathophysiology and risk stratification	- The exact proportional contribution of paradoxical embolism vs. in-situ thrombosis vs. atrial cardiopathy is unclear. - Observational studies link large shunt size to higher stroke risk, but RCT data are contradictory. - It is difficult to distinguish a pathogenic PFO from an incidental finding in an individual patient.	- Prospective mechanistic studies using advanced imaging (OCT, CMR) and tissue sampling to identify thrombus origin. - Genetic and biomarker research to identify patients with endothelial dysfunction and thrombogenic PFOs. - Development of composite risk models that integrate clinical (RoPE score), anatomical (shunt size, ASA), and biomarker data, potentially using AI.
Diagnostic standardization	- The Valsalva maneuver and bubble study methodology are not standardized across TEE, TTE, and TCD, leading to variability. - The diagnostic sensitivity for small or complex PFOs, especially in the elderly, is not well-defined.	- Large multicenter studies to compare imaging modalities with standardized protocols. - Research to establish validated cut-off values for shunt size and tunnel length that correlate with stroke risk.
Management and indications for closure	- Optimal management for elderly patients (>60 years) with cryptogenic stroke and PFO is debated. - The benefit of closure for non-stroke indications (e.g., migraine, decompression sickness) is not firmly established. - The optimal post-closure antithrombotic regimen (antiplatelet vs. anticoagulation) is unclear, especially for those with atrial cardiopathy.	- RCTs focused on high-risk subgroups (e.g., older patients, specific migraine profiles, divers) to clarify who benefits from closure. - Comparative effectiveness studies of different antithrombotic regimens post-closure. - Long-term registries to track the safety and efficacy of new bioabsorbable occlusive devices.
PFO and migraine	- The physiological link between RLS, vasoactive substances (e.g., serotonin), and cortical spreading depression is not fully understood. - PFO closure provides inconsistent relief for migraine, and it is unclear which patients are likely to respond.	- Research into the mechanisms of vasoactive chemicals and cortical spreading depression in PFO-related migraine. - "Enrichment" studies (e.g., the RELIEF trial) to identify biochemical or imaging biomarkers that predict a positive response to closure.
Non-stroke implications	- There is limited prospective evidence on whether PFO closure improves conditions like OSA, decompression sickness, or HAPE.	- Randomized/interventional trials to assess the impact of closure on cardiopulmonary parameters in OSA, dive risk in divers, and acclimatization at high altitude.
Long-term safety	- Long-term data (>5 years) on device safety, risk of late-onset arrhythmias, and the biological impact of device materials on cardiac tissue are scarce.	- Establishment of long-term device registries and post-market surveillance studies to monitor rates of late complications, device erosion, and nickel hypersensitivity.
Clinical integration	- Lack of practical, integrated clinical algorithms that guide clinicians from diagnosis to personalized management recommendations.	- Development of updated, evidence-based consensus guidelines (e.g., via Delphi method) that incorporate novel biomarkers, imaging characteristics, and recent trial data.

PFO: patent foramen ovale; RCT, randomized controlled trial; OCT: optical coherence tomography; CMR: cardiac magnetic resonance; RoPE Score: Risk of Paradoxical Embolism Score; ASD: atrial septal aneurysm; AI: artificial intelligence; TEE: transesophageal echocardiography; TTE: transthoracic echocardiography; TCD: transcranial Doppler; R-L shunt: right-to-left shunt; OSA: obstructive sleep apnea; HAPE: high-altitude pulmonary edema.

Medical Management Versus Interventional Management

PFO closure decreases the incidence of recurrent stroke by 50% to 77% in high-risk patients, as shown by the CLOSE, REDUCE, and DEFENSE-PFO studies. Monotherapy with antiplatelet agents is appropriate for a low-risk PFO (little shunt, no ASA). Anticoagulation (DOACs/warfarin) is not more effective than antiplatelet therapy for PFO-related stroke, according to the ARCADIA study.

Post-Closure Considerations

The risk of AF is around 5% to 10% after closure, with a peak incidence occurring during the first 3 months. Residual

shunt develops in 5% to 10% of cases and requires follow-up imaging. Prolonged surveillance: Continuous antiplatelet medication is often advised.

Additional PFO-Related Conditions (Insufficient Evidence for Closure)

No definitive advantage of closure in randomized controlled trials for migraine with aura (PRIMA, PREMIUM). Decompression sickness: Evaluate the need for closure in divers experiencing severe episodes and possessing a high-grade shunt. OSA: A PFO may exacerbate hypoxia; however, the efficacy of closure remains under research.

CONCLUSIONS

PFO is a common cardiac anomaly that has important and complex implications for stroke risk, particularly in younger adults who lack conventional vascular risk factors. While the majority of individuals with PFO are asymptomatic, certain patients—especially those exhibiting high-risk anatomical characteristics or a history of CS—may benefit from focused diagnostic assessment and, if indicated, percutaneous closure. The complex relationship between PFO and neurological, cardiopulmonary, and systemic conditions presents ongoing clinical opportunities and controversies. Despite significant advancements in management strategies, critical questions persist concerning patient selection, the relevance of anatomical variations, and the ideal equilibrium between medical and interventional methods. Future research concentrating on mechanistic pathways, the standardization of diagnostic protocols, and long-term outcome data will be crucial for refining guidelines and personalizing care. Enhanced comprehension and interdisciplinary cooperation will facilitate more precise risk stratification and improved prevention of PFO-related embolic events.

AUTHORS' CONTRIBUTION

All authors have significantly contributed to the work, whether by conducting literature searches, drafting, revising, or critically reviewing the article. They have given their final approval of the version to be published, have agreed with the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

SOURCES OF FUNDING

None.

CONFLICT OF INTEREST

None.

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