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# Patent Foramen Ovale and Stroke

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## Abstract

Stroke is defined as ''cryptogenic'' when a cause can not determined in the diagnostic work-up. It has been demonstrated that cryptogenic strokes account approximately 25% of ischemic strokes. Patent Foramen Ovale (PFO) is a common interatrial structure, which is reported the prevalence approximately 25% in general population. PFO is observed up to 40% of patients with cryptogenic stroke and its prevalence is higher in younger patients. Currently, many studies and authors have been hypothesized that the relationship between PFO and cryptogenic stroke is related to paradoxical embolism via right-to-left atrial shunting of a clinically latent thrombi. The primary prevention for stroke is not recommended in patients with PFO. Antiplatelet or anticoagulan therapy are recommended to all cryptogenic stroke patients with PFO. In these patients, recurrent stroke or TIA are observed despite medical therapy in follow-up. Three large randomized controlled trials comparing percutaneous closure of PFO with medical therapy have not demonstrated clear clinical benefit in terms of recurrent stroke or TIA. Therefore, PFO closure should be considered only in younger patients with PFO and cryptogenic stroke, especially who have anatomical and hemodynamic risk factors such as more than moderate right-to-left atrial shunt and the presence of ASA. Finally, all of these studies indicate that optimal medical therapy and careful patient selection for percutaneous closure of PFO at individual patients.

**Keywords: Patent foramen ovale; Stroke; Shunt**

## Introduction

Stroke is one of the most common causes of the mortality and disability in the worldwide. The frequency of stroke is markedly increasing recently. Among all strokes, a very large proportion are ischemic and cryptogenic strokes are considered to consist about 25% of all ischemic strokes [1]. Cryptogenic stroke is defined that its cause is not identified at end of the etiological investigation. Most cryptogenic strokes are thought to originate from any of various well-known potential embolic sources such as low-risk or confidential cardiac sources (e.g., valvular calcification), paradoxical embolism, and non-occlusive atherosclerotic plaques in the aortic arch or cervicocerebral arteries [2]. The foramen ovale is an important fetal structure that normally closes after birth in most neonates. However, in some individuals, it will fail to close completely, which is called as a patent foramen ovale (PFO) [3]. The prevalence of PFO is approximately 25% in healthy people. This PFO prevalence appears to be higher in young people on imaging and autopsy studies, with 34% prevalence at age <30 years, 25% at age 30 to 80, and then 20% at age >80 [3]. Patients with PFO do not usually have any problem throughout all lifetime. But rarely, PFO has been associated with decompression illness, platypnea-orthodeoxia syndrome, migraine headaches, and obstructive sleep apnea [4]. On the other hand, it has been demonstrated that PFO is found up to 40% in patients with cryptogenic stroke especially in younger patients [3,5]. It is shown that the relationship between PFO and stroke is related to paradoxical embolism which is originated from shunt of the right atrium to the left atrium [6,7]. In 1988, Lechat et al. first suggested that PFO may cause to the stroke due to paradoxical embolism in patients with clinically latent venous thrombosis [8]. As there is controversial results in previous studies, the association between PFO and first or recurrent stroke is not clear yet. However, several factors including presence of Atrial Septal Aneurysm (ASA), severity of the right-to-left atrial shunt during resting condition or Valsalva maneuver, and younger age are associated with increased risk of cryptogenic stroke in patients with PFO [9]. In this review, we shortly focused on the relationship between PFO and stroke, which include the diagnosis of PFO, its association, and management strategies.

## Diagnosis of Patent Foramen Ovale

Ultrason-based imaging modalities are crucial for the diagnosis of a PFO and the presence of right-to-left atrial shunts. Transcranial Duplex (TCD), Transthoracic (TTE) and Transesophageal

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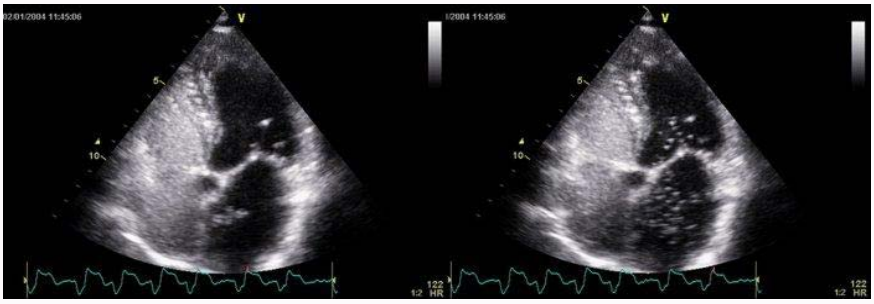

**Figure 1:** A patent foramen ovale with agited saline bubble study that shows right-to-left atrial shunting in the transthoracic echocardiography.

(TEE) echocardiography are avaliable the main techniques for PFO diagnosis and risk stratification. The agited saline microbubble study into a peripheral vein, is used as a gold standart test for the diagnosis and assessment of shunt severity of PFO in all these ultrasound techniques [10]. The microbubble study should be done under rest and then provocative maneuvres including Valsalva and coughing, which cause increasing of the right atrial pressure and facilitate the PFO opening. The initial diagnostic test is TTE with use of agited saline microbubble study (Figure 1). TTE has important advantages including widespread availability, non-invasive, cost-effective, and safety. TTE shows with high accuracy the cardiac structural abnormalities, interatrial septum, ASA and other right atrial structures such as prominent Eustachian valve and Chiari network. Since TTE usually does not show directly the PFO, microbubble study should be used with provocative maneuvres. Thus, it has demonstrated useful for diagnosis and evaluation of the shunt amount, with a high sensivity equivalent to TEE in the detection of PFO [11,12]. During the microbubble study in normal rest condition and Valsalva maneoeuvre, if the bubbles are seen in the left atrium within 3 cardiac cycles, it means that the peresence of intracardiac shunt as a PFO [13]. If the bubbles are seen in the left atrium after 5-6 cardiac cycles, it should be considered that the presence of a pulmonary arteriovenous malformation [13]. TEE is gold standart in the diagnosis of PFO with a very high sensivity and specifity. In a study, it has demonstrated that sensivity and specifity of agited saline TEE, 89% and 100%, respectively. TEE shows not only bubbles in the left atrium, also allows clear visualization of the PFO location and size with atrial septum anatomy. In addition, it shows that visualization of the bubbles crossing the PFO and the presence of the right-to-left atrial shunt with use of Doppler color flow imaging. The microbubble study should be done in TEE as well as TTE. This provides more accurate results and is the best diagnostic tool. In the TTE or TEE examination, semi quantification of right-to-left shunt is detected by the number of bubbles visualized to transit into the left atrium on bubble study. It is classified: a small shunt 3-10 bubbles, a moderate shunt 10-20 bubbles, and a large shunt >20 bubbles in the left atrium [14]. Both grade of shunting and shunt direction can vary due to physiologic condition of patient, the location of agited saline injection and able to perform Valsalva maneuver. Thus, sedation administered during TEE may comprise an effective Valsalva maneouvre or coughing. It causes to underestimate a potential shunt presence and severity [15]. TCD is based on the intracranial detection of injected agited saline microbubbles [16]. This test shows right-to-left shunt by detecting of hyperintense signals in the Doppler spectrum of middle cerabral artery flow velocity [16]. It is likely even more sensitive than TEE for detecting absolute right-to-left shunt, but it does not give information about atrial septum, structure of right atrium and PFO. Additionally, TCD can not differentiate intracardiac shunts from intrapulmonary shunts, compared with echocardiography [17]. Other techniques such as Computed Tomography (CT) and Magnetic Resonance İmaging (MRI) do not provide additional diagnostic information for PFO. The use of microbubble study can be very difficult in these tests, also they are not cost-effective and avaliable. So, their use in clinical practice is not recommended in diagnostic work-up of PFO [18].

## The Relatıonshıp Between Patent Foramen Ovale And Stroke

A stroke is deemed ''cryptogenic'' when a specific cause has not been found in the etiologic work-up. Cryptogenic strokes are approximately 30% of overall strokes and more common in younger patients [19]. The majority of overall stroke incidence appears in patients aged >55 years old with a high risk of recurrence of 14-25%, but patients <45 years old with stroke is upwards of 40% cryptogenic and also represent with risk of recurrence of 10% [20]. Many previous studies have been demonstrated the relationship between PFO and cryptogenic stroke [21-24]. Currently, they have been thought that the paradoxical embolism through PFO is responsible for stroke. They have hypothesized that in these individuals, a clinically latent venous thrombosis or clot passes to systmemic arterial circulation via shunting from the right atrium to the left atrium. However, prospective studies have not clearly shown an association, and PFO is an independent predictor of stroke in the general population [25,26]. These results suggest that the development of stroke in patients with PFO is likely multifactorial with contributions from other factors. On the other hand, the prevalence of PFO is high in general population and only a small number of these people may have also an additional risk factor that increases the risk of stroke. Although PFO is seen up to 40% of patients with cryptogenic stroke, it is thought that in most cases the role PFO in stroke is only probabilistic. The probability means that when a PFO found in the setting of a cryptogenic stroke, the stoke is reliably related to PFO vs. other risk factors such as age, hypertension, hyperlipidemia and diabetes mellitus [27]. Therefore, it has been studied to identify the patient features that may be important in therapeutic decision-making in patients with PFO and stroke. Kent et al. [28] have found a Risk of Paradoxical Embolism (RoPE) score, which helps to reliably assess the probability of stroke related to PFO and rate of recurrent stroke or Transient İschemic Attack (TIA) in patients with cryptogenic stroke [28]. They developed the 10-point based RoPE score with using clinical variables and brain imaging characteristics of 12 large studies (Table 1) [28]. There have many parameters including absence of risk factors (no history of hypertension, no history of diabetes mellitus, no smoking and no history of previous stroke or TIA), age and cortical brain infarct in the RoPE score index [28]. The RoPE score can easily apply for

**Table 1:** The Risk of Paradoxical Embolism (RoPE) score.

| Characteristic | Score Point |
|---|---|
| No history of hypertension | 1 |
| No history of diabetes mellitus | 1 |
| No history of stroke or TIA | 1 |
| Non-smoker | 1 |
| Cortical infarct on imaging | 1 |
| Age (years) | |
| 18-29 | 5 |
| 30-39 | 4 |
| 40-49 | 3 |
| 50-59 | 2 |
| 60-69 | 1 |
| ≥70 | 0 |
| Total score (sum of individual points) | 0-10 point |

every patient in clinical practice. If a patient with cryptogenic stroke has a high RoPE score, it means that stroke presumably is related to PFO, but also importantly this patient has lower the risk of recurrent stroke or TIA. However, the RoPE score index does not include the anatomic characteristics of PFOs and hemodynamic features of right-to-left atrial shunts. But, in previous studies there have been determined some anatomical and hemodynamic characteristics, that are associated with increased risk of cryptogenic stroke. These are a large PFO (>10mm), a PFO with long tunnel lenght >10mm, PFO size, moderate to large right-to-left atrial shunt especially in resting conditions, the presence of ASA, and the presence of right atrial structures such as prominent Eustachian valve and Chiari network [29,30]. Among these, importantly the presence of ASA with PFO may be an independent factor risk factor for ischemic stroke, particularly in those patients <55 years. In addition, some laboratory findings may be used to predict recurrent stroke in patients with PFO and cryptogenic stroke. It was shown that a high D-dimer level was associated with increased risk of recurrent ischemic stroke in patients with PFO-related stroke [31]. The risk of stroke or TIA increases more than three-fold in patients with PFO after pacemaker wire implantation. Interestingly, it has been demonstrated that in patients with PFO who have no history of other cardioembolic risk factors, the posterior brain circulation involvement was shown more than patients with aortic arch plaque or paroxysmal atrial fibrillation [32]. In this context, one brain CT study demonstrated that the amount of blood flow in the posterior circulation was higher than the anterior circulation during Valsalva maneuvre [33]. This may be an explanation for the posterior predominance of paradoxical embolism. Silent small cortical infarcts may seen in patients with PFO. These are associated with subclinic deficits and increased risk of dementia due to cognitive impairment [34]. In a prospective study, which evaluated the presence of paradoxical embolism in healty people with silent brain infarcts, significant right-to-left atrial shunt was shown in 51% of study population [35]. Therefore, it should be absolutely worked on diagnosis of PFO in younger patients with silent small cortical infarcts and absence of other risk factors.

# Management

## Medical therapy

Currently, medical therapy is not recommended for primary prevention of stroke in patients with PFO [36]. Optimal management of paradoxical embolism is not clear yet. The patients with PFO and cryptogenic stroke should be treated with antiplatelet therapy, since its benefit and safety has been shown in previous studies [17,37]. But, in those patients, anticoagulation therapy is recommended in the presence of another indication for anticoagulation such as atrial fibrillation, deep venous thrombosis, and hypercoagulable conditions. In addition, anticoagulation also may be considered in patients who have experienced recurrent stroke or TIA under antiplatelet therapy. Currently, many authors have been hypothesized that explanation of stroke in patients with PFO is paradoxical embolism of a small thrombi or clot from right atrium to the left atrium [6,7]. Therefore, it has been thought that anticoagulation therapy may be decrease the rate of recurrent stroke and TIA in these patients. The PFO in Cryptogenic Stroke Study (PICCS) is a randomized controlled trial that comparing aspirin with warfarin therapy for secondary stroke prevention [38]. PICCS study did not show any statistically significant difference in the primary composite endpoint of recurrent stroke or death at 2 years between the two groups [38]. In another very small single-center randomized controlled study which compared the warfarin with aspirin in patients with cryptogenic stroke, there were no differences between the two groups in terms of ischemic stroke, TIA and mortality. A meta-analysis including these small trials, showed that warfarin therapy might be favor, but also others demonsrated no benefit of anticoagulation over antiplatelet therapy [37,39]. Overall, it is still controversial that warfarin is superior to antiplatelet therapy in preventing recurrent ischemic stroke events. Currently, the use of novel oral anticoagulants in cryptogenic stroke patients are studying in some trials, which is an attractive option for optimal medical therapy [40].

## Percutaneous closure

Although percutaneous closure of PFO has become very intriguing in invasive cardiology now, the efficacy and safety of PFO closure is controversial. The procedural success rate of percutaneous closure is very high (>90%) and the antiplatelet therapy is recommended at least 6 months after procedure in these patients. However, the percutaneous closure is an expensive treatment and complication rate of procedure is not low (approximately 5-10%) with risk of early recurrent ischemic stroke. In previous observational studies generally observed that PFO closure reduces the risk of recurrent stroke or TIA. Then, three large randomized controlled clinical trials comparing percutaneous PFO closure with medical therapy have been published recently. The Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale (CLOSURE I) trial enrolled 909 patients younger than 60 years of age with cryptogenic stroke or TIA randomised to a medical therapy or percutaneous closure using the StarFlex closure device [41]. In CLOSURE I trial, there was no statistically significant difference between the two groups in primary composite endpoint of recurrent stroke and TIA, or 30 day mortality at a mean follow up of two years [41]. Atrial fibrillation and vascular complications were observed more in the PFO closure group [41]. The Randomized Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism (PC) trial enrolled 414 patients younger than 60 years of age with PFO and cryptogenic stroke or TIA randomised to a medical therapy or PFO closure with Amplatzer closure device [42]. The PC trial did show no difference in the primary endpoint, a composite of death, nonfatal stroke, TIA, or peripheral embolism between the medical therapy group and PFO closure group ( 5.2% vs. 3.4%, p=0.34, respectively)

[42]. The Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke (RESPECT) trial randomized 180 patients with PFO and cryptogenic stroke to a medical therapy or percutaneous PFO closure [43]. In RESPECT trial, there was no difference in the primary composite outcome of recurrent ischemic stroke, stroke mortality or early mortality at two years follow-up [43]. But, the subgroup analysis of RESPECT trial demonstrated that PFO closure may improve the primary composite outcome in patients with a large right-to-left atrial shunt or an ASA. ( p=0.02 and p=0.01, respectively) [43]. A recent prospective observational study enrolled 158 consecutive patients comparing PFO closure with medical therapy [44]. The primary endpoint was a composite of recurrent stroke and TIA at a mean follow-up of 28 months and there was significantly difference between the two groups (p=0.039) [44]. This study showed that PFO closure may be an effective treatment to prevent recurrent stroke or TIA in selective patients with right-to-left atrial shunt more than moderate grade [44]. The results of all of these studies were not confirm the superiority of PFO closure to medical therapy. Therefore, PFO closure is not currently recommended as first-line treatment option for secondary prevention in patients with PFO and cryptogenic stroke. The percutaneous closure of PFO may be considered especially in selective patients younger than 55 years of age, who have more than moderate right-to-left atrial shunt and ASA.

## Conclusıon

PFO is a common interatrial septal anomaly, which is reported the prevalence in about 25% of general population and it is believed that this PFO prevalence may be higher on imaging and autopsy studies especially in young patients [19]. A stroke is defined cryptogenic when an etiologic cause has not been detected. Cryptogenic strokes are now thought to comprise approximately 30% of all strokes and PFO can be observed up to 40% in patients with cryptogenic stroke [3,5]. Currently, it has been hypothesized that the relationship between PFO and cryptogenic stroke is related to paradoxical embolism via right-to-left atrial shunting of a clinically latent thrombi [6,7]. Antiplatelet or anticoagulation therapy are recommended to all patients with PFO and crytogenic stroke. In these patients, recurrent stroke or TIA are observed despite medical therapy. Three large randomized controlled trials comparing percutaneous closure of PFO with medical therapy have not demonstrated clear clinical benefit in terms of recurrent stroke or TIA [41-43]. Therefore, PFO closure should be considered in younger patients with PFO and cryptogenic stroke, especially who have anatomical and hemodynamic risk factors such as more than moderate right-to-left atrial shunt and the presence of ASA. Overall, all of these trials results indicate that careful patient selection and treatment for individual patients.

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