Patent Foramen Ovale and Stroke—Current Status

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Introduction

Cryptogenic (of unknown cause) ischemic strokes are now thought to comprise approximately 25% of all ischemic strokes. Most cryptogenic strokes are thromboembolic (embolic stroke of undetermined source [ESUS]). The thrombus is thought to originate from any of several well-established potential embolic sources, including minor-risk or covert cardiac sources (e.g., mitral annular calcification), veins via paradoxical embolism, and non-occlusive atherosclerotic plaques in the aortic arch or in the cervical or cerebral arteries.1

The foramen ovale is a hole that exists in the wall between the left and right atria of every human fetus. It normally closes during infancy. The foramen ovale does not close in approximately 25% of the general population (Figure 1). Most patients do not have any problems with patent foramen ovale (PFO), although blood is leaking from the right atrium to the left atrium (LA). Problems can arise when that blood contains a blood clot. Lechat et al.2 first called attention to PFO and stroke in 1988. They suggested that because of the high prevalence of clinically latent venous thrombosis, paradoxical embolism through PFO might be responsible for stroke more often than is usually suspected. Subsequent studies showed that PFO can be found in up to 40% of patients with ESUS.3,4

Until now, whether PFO is a risk factor for stroke has been unsettled. Results about the association of PFO with first stroke4,5 and with recurrent stroke6,7 have been controversial. Several factors possibly associated with increased risk of stroke recurrence in patients with PFO include a right-to-left shunt (RLS) detectable in resting conditions,8 amount of RLS under Valsalva,9 and a combination of PFO with either atrial septal aneurysm (ASA) or increased interatrial septal mobility.6 However, such findings were not confirmed in other studies.7,10 Despite these controversial results, interest in PFO has emerged recently because of a renewed focus on ESUS, especially in younger patients, technical advances in the diagnosis of PFO, and the emergence of endovascular device closure as a treatment option.8,11
Diagnosis of patent foramen ovale

Various tools can be used to detect PFO and RLS (Figure 2). Transesophageal echocardiography (TEE) is considered the gold standard in the evaluation of ESUS. By TEE, the PFO size and concomitant existence of ASA, which are critical in defining high-risk PFO, as well as the possible existence of an intrapulmonary shunt\textsuperscript{12,13} may be confirmed. However, routine application of TEE is often limited in patients with acute stroke because of acute illness, mental changes, coagulopathy/bleeding tendency, and lack of patient cooperation. Echocardiography is also dependent on the properties of the equipment and on the expertise of the investigator. Agitated saline transcranial Duplex (TCD)
monitoring is based on the intracranial detection of intravenously injected microemboli. The Valsalva maneuver is much easier when the agitated saline TCD technique is performed. Therefore, the size and functional relevance of RLS can more easily be assessed using TCD than TEE. The TCD technique has a similar sensitivity and specificity as TEE. The agitated saline TCD technique is reportedly safe in patients with ESUS being evaluated for RLS detection. RLS can also be detected noninvasively using dye dilution or ear oximetry methods with high sensitivity and specificity when compared with TEE. Recently, cardiac computed tomographic angiography was used to confirm the presence of a PFO with high accuracy.

The probability of having PFO as a cause or coincidence of stroke

In patients with ESUS, one-third of discovered PFO are likely to be incidental and, hence, not benefit from closure, while PFO could be pathogenic in certain situations. The probability that a PFO discovered in the setting of an ESUS is stroke-related vs. incidental depends on the patient’s age, presence of traditional risk factors, and type of cerebral infarct. Therefore, there have been efforts to identify the patient characteristics that may be important in patient selection in therapeutic decision-making. Kent and colleagues recently reported that younger patients without vascular risk factors are much more likely to have PFO than patients without risk factors. Using the clinical and brain imaging features, they suggested the 10-point Risk of Paradoxical Embolism (RoPE) score. If a patient with ESUS shows a high RoPE score, it is likely that ESUS is attributable to PFO (Figure 3). Beside the clinical and brain imaging features, laboratory findings may be useful for predicting outcomes and determining a treatment strategy. One recent study showed that the coexistence of PFO and a high D-dimer level increased the risk of recurrent ischemic stroke in patients with PFO-related stroke.

Patients with ESUS show distinct clinicoradiological features depending on the underlying causes: aortic arch atheroma, PFO, and paroxysmal atrial fibrillation. Other authors and we have shown that patients with PFO had healthy vascular risk factor profiles and displayed posterior circulation involvement compared to patients with aortic arch atheroma or paroxysmal atrial fibrillation. One brain single-photon emission computed tomography study showed that during the Valsalva maneuver the rate of blood flow in the posterior circulation was higher than that in the anterior circulation, which could be a possible explanation for the posterior predominance of paradoxical embolism. We have reported that stroke phenotypes differed among patients with stroke and PFO and that the amount of RLS determined the lesion patterns on diffusion-weighted imaging (DWI); most patients with massive RLS showed small infarcts upon DWI, whereas large infarcts were observed in more than 40% of patients with mild amounts of RLS. These results suggest that mechanisms of stroke other than the paradoxical mechanism may play an important role in patients with large embolic stroke (Figure 4). However, controversial results exist in the association of DWI lesion characteristics and the PFO size, and the presence of deep vein thrombosis and interatrial septal abnormalities (ASA and septal excursion distance) were also associated with a large brain infarct.

Although the risk of stroke recurrence is low in patients with PFO-related stroke (Figure 3), the biological relevance of PFO is unknown. PFO could be the cause of silent brain infarcts (Figure 5). Silent infarcts are associated with subtle deficits and increase the risk of subsequent stroke and dementia by approximately two-fold. Compared to small vessel disease, silent brain

Figure 3. The Risk of Paradoxical Embolism (RoPE) score and the risk of stroke recurrence. Modified from Calvet and Mas.
Infarcts associated with cardiac disease are underrecognized. Both PFO and PFO closure are reportedly associated with silent brain infarcts. The influence of cerebral emboli caused by PFO on white matter lesions and cognitive impairment has been reported. In the ICONS (Identification of the Cause of Silent Cerebral Infarction in Healthy Subjects) study, which prospectively evaluated the presence of paradoxical embolism in healthy subjects with silent brain infarcts, RLS was observed in 51%. Therefore, PFO should be considered in young patients with superficially located silent infarcts and relatively healthy risk profiles.

**Prevention of stroke in patients with PFO-related stroke**

Paradoxical embolism has been considered a main mechanism of stroke in patients with PFO. Paradoxical embolism was considered a possible diagnosis if there was an arterial embolism without demonstrable sources; coexistence of deep venous thrombosis, pulmonary embolism, or cough/other Valsalva maneuver immediately preceding the onset of stroke symptoms; and an RLS. However, in the prospective Spanish multicenter Right-to-Left Shunt in Cryptogenic Stroke (CODICIA) study, there was no association between massive RLS and recurrent stroke. Clinical conditions, such as prothrombotic conditions (deep vein thrombosis, prolonged immobility/postoperative period, and the Valsalva maneuver), are often considered as clinical indicators of paradoxical embolism. However, in data from the Tufts PFO registry, these features were not associated with embolism recurrence. Moreover, deep vein thrombosis is infrequently detected in patients with ESUS and PFO.

In addition, controversy remains regarding the benefit of percutaneous closure of PFO among patients with ESUS. Three randomized controlled trials of the management of patients with ESUS and PFO have been reported recently (Table 1): the Evaluation of the STARFlex Septal Closure System in Patients With a Stroke and/or Transient Ischemic Attack Due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale (CLOSURE I), the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT), and the Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism (PC Trial). All three randomized clinical trials failed to demonstrate superiority of closure compared with medical treatment. In the CLOSURE I trial, PFO closure increased the risk of new-onset atrial fibrillation. These failures may be caused by inappropriate patient selection (many patients had transient ischemic attacks rather than superficial infarcts), wrong devices (procedural failure > 10%), or wrong study design (unblinded and selection bias) but also could be caused by a limitation in the efficacy of PFO closure in patients with ESUS and PFO. Low annual risk of recurrent stroke in patients with PFO-related stroke might be considered for the determination of therapeutic options. The complication rates were different depending on the
Figure 5. Silent small cortical infarcts in patients with PFO. (A) A 50-year-old apparently healthy man underwent brain MRI for a medical check-up. The MRI showed multiple small ischemic changes on bilateral centrum semiovale on a fluid-attenuated inversion recovery (FLAIR) image. A transcranial Doppler agitated saline test revealed a right-to-left shunt. (B) A 75-year-old woman underwent MRI for the purpose of preoperative evaluation for stroke risk. Incidental findings included multiple small acute infarcts involving multivascular territories on diffusion-weighted imaging (DWI). Transesophageal echocardiogram revealed a normal aorta but an intracardiac shunt. (C) A 62-year-old apparently healthy woman with a history of migraine headaches underwent brain MRI for her chronic headaches. MRI showed multiple silent but acute small cortical infarcts on DWI (upper image) and silent small cortical infarcts on FLAIR (lower image).

Table 1. Results of clinical trials of PFO closure

| Inclusion Groups | CLOSURE I (2012) | RESPECT (2013) | PC (2013) |
|------------------|-----------------|---------------|-----------|
| 1. Closure device | Stroke or TIA   | Stroke or TIA, peripheral TE | Stroke or TIA, peripheral TE |
| 2. Medical arm   | STARFlex, Aspirin, warfarin | Aspirin, clopidogrel, aggrenox, warfarin | Aspirin, ticlopidine, clopidogrel, warfarin |
| Outcome          | 2 years, Death, stroke or TIA | 8 years, Death, stroke or TIA, peripheral TE | 4 years, Death, stroke or TIA, peripheral TE |
| Primary end point, HR (95% CI) | 0.78 (0.45-1.35) | 0.63 (0.24-1.62) | 0.63 (0.24-1.62) |
| Stroke or TIA, HR (95% CI) | 0.82 (0.38-1.76) | 0.49 (0.22-1.11) | 0.45 (0.18-1.29) |
| New-onset AF, OR (95% CI) | 9.11 (2.71-30.58)* | 1.93 (0.17-21.37) | 3.15 (0.63-15.800) |

*P<0.05.

TIA, transient ischemic attack; TE, thromboembolism; M, medical arm; C, closure arm; HR, hazard ratio; OR, odds ratio; CI, confidence interval; AF, atrial fibrillation.
device types (STARFlex vs. Amplatzer) used in the clinical trials. Development of a newer device with a higher procedural success rate and fewer proarrhythmic effects is needed.

In a prospective study of PFO closure, although patients with large RLS received percutaneous closure, older age, multiple previous strokes, and ASA but not PFO closure were associated with stroke or mortality. Therefore, although most studies have focused on PFO closure, the mechanisms of stroke other than paradoxical embolism may be important in patients with ESUS and PFO (Figure 6). First, migraine is commonly found in patients with PFO and is a risk factor for some etiopathogenic subtypes of cerebral infarcts such as dissections and PFO. A recent Duplex study showed that migraineurs have isolated cerebral endothelial dysfunction restricted to the posterior circulation in the absence of systemic endothelial dysfunction. Second, occult atrial fibrillation (AF) may exist in patients with ESUS and incidental PFO. LA dysfunction could be a marker of incident AF, atrial thrombi, and thromboembolic risks of AF. The LA functions of PFO patients were reportedly lower than normal, similar to patients with AF. In addition, increased incidence of interatrial block due to stretching of the interatrial septum was reported in patients with ESUS and PFO, suggesting that atrial rhythmia might underlie and mediate thrombus formation. Because atrial dysfunction and concomitant AF have been suggested as a mechanism of stroke related to PFO, longer electrocardiogram monitoring should be considered for patients with larger infarcts or echocardiographic findings of LA dysfunction.

Finally, thrombus within the ASA or LA may contribute to arterial embolism. Cardiac thrombus formation secondary to localized hypercoagulable conditions related to structural changes in the LA, left atrial appendage, and ASA have been suggested as potential mechanisms for stroke. Using intraprocedural intracardiac echocardiographic assessment in candidates for PFO closure, Rigatelli and colleagues demonstrated that ASA were associated with LA dysfunction, and spontaneous echo contrast was observed in 52% of ASA. This may be true for patients without ASA. Recently, reports about the association between LA abnormality and cryptogenic stroke have been increasing. LA enlargement related to PFO and RLS might precipitate incident and recurrent embolism from PFO in the absence of overt LA dysfunction.

The American Heart Association/American Stroke Association recently recommended treatment guidelines in patients with PFO and ESUS (Table 2). Data to establish whether anticoagulation is superior to aspirin for secondary stroke prevention in patients with PFO are insufficient. Randomized controlled trials comparing non-vitamin K antagonists versus antiplatelet agents in patients with ESUS are ongoing (Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source [RE-SPECT ESUS], NCT02239120, and Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source [NAVIGATE ESUS], NCT02313909).

**Conclusion**

PFO is an important risk factor for ESUS. PFO could be a cause or coincidence of stroke. In addition, PFO closure could

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**Table 2.** Guideline for second prevention of stroke in patients with patent foramen ovale

| Recommendation | Class | Level of Evidence |
|---------------|-------|-------------------|
| There are insufficient data to establish whether anticoagulation is equivalent or superior to aspirin for secondary stroke prevention in patients with PFO | Class IIIb; Level of Evidence B |
| For patients with an ischemic stroke or TIA and a PFO who are not undergoing anticoagulation therapy, antiplatelet therapy is recommended | Class I; Level of Evidence B | (Revised recommendation) |
| For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics | Class I; Level of Evidence A |
| When anticoagulation is contraindicated, an inferior vena cava filter is reasonable | Class IIa; Level of Evidence C | (New recommendation) |
| For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for deep vein thrombosis, available data do not support a benefit for PFO closure | Class III; Level of Evidence A | (Revised recommendation) |
| In the setting of PFO and deep vein thrombosis, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent deep vein thrombosis | Class IIIb; Level of Evidence C | (New recommendation) |

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Figure 6. Possible mechanisms of stroke in patients with PFO.

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be helpful but also could be harmful (arrhythmogenic). The PFO attributable fraction as well as stroke mechanisms (paradoxical embolism vs. others) may differ greatly among patients. Further advances in our understanding of stroke mechanisms are needed together with advances in closure devices. In the meantime, therapeutic approaches tailored to the patient’s characteristics are needed.

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