PFO as Seen From the Brain

A neurological view of patent foramen ovale and closure.

BY LARS THOMASSEN, MD, PhD, AND ULRIKE WAJE-ANDREASSEN, MD, PhD

Patient foramen ovale (PFO) is found at autopsy in 27% of the general population, declining from 34% in patients during the first 3 decades of life to 20% in older patients. Cryptogenic ischemic stroke without an identifiable cause accounts for 25% of all ischemic strokes and up to 50% in young stroke patients. PFO has been associated with cryptogenic stroke, and paradoxical embolism across a PFO is one potential cause for these strokes. PFO has been associated with migraine. There is an abundance of case series, personal opinions, editorials, and review articles on PFO, but the management of patients with PFO remains a matter of dispute. In the face of uncertainty, our strategy should be to place more patients into randomized controlled trials. This article aims to discuss PFO and stroke from a neurovascular viewpoint.

THE BRAIN

Cerebral Infarct

Acute cerebral infarct is a heterogeneous clinical syndrome with multiple etiologies but with vascular occlusion as a common denominator. The diagnosis of acute ischemic cerebrovascular disease has traditionally been based on clinical symptomatology. Today, magnetic resonance imaging (MRI) and duplex ultrasonography have turned toward diagnosing underlying pathophysiology and disease mechanisms. Approximately 20% of patients have ischemia caused by emboli from the heart, 20% from emboli or hypoperfusion related to the precerebral arteries, and 25% from nonembolic occlusion of small cerebral perforating arteries. In 30% to 40% of patients, the exact cause of infarct cannot be determined (cryptogenic infarct). Clinical discrimination between different pathophysiological groups is unreliable. Forty percent of patients presenting with neurological deficits suggestive of perforating artery disease have embolic infarcts that can be seen on diffusion-weighted MRI (DW-MRI) (Figure 1). Additional ultrasound and angiographic examinations are needed to detect atherosclerotic disease (Figure 2). Therefore, an extensive diagnostic workup of the acute stroke patient is mandatory. In PFO studies, computed tomography is inadequate, and MRI is the gold standard for brain imaging.

Transient Ischemic Attack

Transient ischemic attack (TIA) classification has traditionally been based on symptom regression over time using arbitrary time cutoffs. TIA remains a highly subjective diagnosis, even among stroke subspecialists. Therefore, the use of confirmatory testing beyond clinical judgment is necessary. DW-MRI studies have shown that approximately half of patients with clinical TIA have an ischemic lesion and that the likelihood of DWI lesions increases with increasing symptom duration. As a result of such neuroimaging findings, the diagnosis of infarct/TIA is increasingly based on tissue pathophysiology rather than time and with imaging sensitive to neu-
ronal injury as biomarkers. Patients with “MRI-veri-
ified TIA” (i.e., clinically transient symptoms with MRI-veri-
ified ischemic lesions) should be the only clinical TIA 
patients allowed to enter a PFO study so that the most 
accurate data can be obtained. However, because very 
few patients who are treated for PFO closure are entered 
into clinical trials, clinicians often choose to close a PFO 
in the absence of MRI data if the clinical scenario and 
other laboratory data are compelling.

Silent Cerebral Infarct
In patients with no history of TIA or stroke, infarcts 
may be present on brain imaging. Although silent 
infarcts lack clinically overt symptoms, they may be 
associated with subtle physical and cognitive deficits, 
which may accumulate over time. MRI-defined silent 
brain infarcts are detected in 8% to 28% of the general 
population, in 20% of healthy elderly people, and in up 
to 51% of patients in selected series. Silent brain 
infarcts are far more common than stroke, both with 
respect to prevalence and incidence. Most silent infarcts 
are lacunes, which are associated with hypertensive 
small-vessel disease. However, the prevalence of silent 
cerebral infarcts is also closely related to the presence 
of PFO, and PFO is an independent predictor of silent 
brain infarcts in patients with pulmonary embolism. 
Therefore, silent cerebral infarcts need careful attention 
in any PFO study, with or without percutaneous inter-
vention.

THE HEART

PFO
A PFO is a gateway from the venous to the arterial 
circulation and to the brain. Contrast-enhanced tran-
scranial Doppler (TCD) sonography can readily identify 
a right-to-left shunt (RLS), with PFO as the most com-
mon site. Intravenously injected echo contrast that is 
unable to pass the pulmonary capillary bed will, in the 
presence of RLS, enter the arterial circulation and pro-
duces microembolic signals during the contrast-enhanced 
TCD recording (Figure 3). This procedure is highly stan-
dardized.

Morphological and hemodynamic features of inter-
trial septum abnormalities may increase the risk of 
embolism. Transesophageal echocardiography (TEE) is 
the gold standard for PFO diagnosis because it allows 
direct visualization of the PFO and additional atrial and 
aortic potential sources of emboli. The final diagnosis 
thereby lies in the hands of cardiologists.

The accuracy of transcranial ultrasonography and 
echocardiography for larger shunts is fairly identical. 
Compared with TEE, TCD has a sensitivity of 90% to 
100% and a specificity of 65% to 94%. Regularly, 
more patients are found to have RLS when investigated 
with TCD compared with TEE. In these cases, the TCD-
detected shunting may reflect more effective Valsalva 
maneuvers or may correspond to extracardiac (pul-
monary) shunts or very small intracardiac shunts not 
noted during TEE. TCD allows a semiquantification of 
the size of an RLS by registering the number/amount of 
microembolic signals and reliably registers even one sin-
gle microembolic signal as an indication of a small 
shunt. However, TCD cannot identify the site of an RLS 
by the number of microembolic signals detected or by 
the time delay before the first microembolic signal. 
Because sensitivity of contrast TCD prevails over speci-
ficity, TCD remains a valuable screening procedure, 
whereas TEE remains necessary for the ultimate diagno-

Figure 2. Carotid duplex ultrasound examination shows a 
normal bifurcation supporting the diagnosis of paradoxical 
emboli (A) and a minimal plaque (arrow) leaving the cause of 
an ipsilateral infarct rather open (B).

Figure 3. Transcranial Doppler monitoring of the middle 
cerebral artery during injection of agitated saline at rest (A) 
or with Valsalva maneuver (B) showing three degrees of RLS. 
Note the flow velocity reduction as an indicator for an effec-
tive Valsalva maneuver.
sies. Contrast-enhanced TCD and TEE are thus complementary methods representing a “combined gold standard” in the assessment of cryptogenic stroke.15

THE HEART-BRAIN CONNECTION

PFO as Potential Cause of Stroke

Cryptogenic stroke in patients with PFO is not equal to paradoxical embolism. Given the high prevalence of PFO in the general population, the PFO may be a “bystander PFO” with no pathophysiological relationship to the index stroke (ie, an incidental and not pathogenic PFO). A systematic review of case-control studies of patients with cryptogenic stroke estimated the probability of PFO being incidental to 33% (28%–39%) in age-inclusive studies, 20% (16%–25%) in younger patients, and 48% (34%–66%) in older patients.19

A meta-analysis of case-control studies has confirmed an increased prevalence of PFO among patients with cryptogenic stroke as compared with stroke of known cause.2 In patients with cryptogenic stroke, a strong association has been found in patients younger than 55 years, and a weaker association has been found in patients aged 55 years or older, compared with subjects with stroke of known cause.19 Therefore, age seems to matter. Although most case-control studies have focused on younger patients, the risk of having PFO in the setting of cryptogenic stroke is also higher in older patients.20 An age-related increase in coagulability, as well as an increased incidence of venous thromboembolism, may contribute to this increased risk.21 Many older patients will nevertheless be classified as having “stroke of unknown cause” due to the presence of several potential causes.

There are factors other than age that affect PFO. For instance, size of the PFO matters.22 Large PFOs are more prevalent in the cryptogenic stroke population than among patients with stroke of known cause, and patients with larger PFOs show more embolic infarcts on brain imaging than those with small PFOs.23 Concomitant pathology also matters.2 PFO together with an atrial septal aneurysm (ASA) are more common in patients with cryptogenic stroke compared with patients with stroke of known cause.20 The combination PFO-ASA is significantly associated with the degree of MRI white matter lesions and with multiple cerebral infarcts.24,26 A large PFO and the combination PFO-ASA may indicate an increased embolic risk, but in individual patients, there is no definitive way to distinguish whether a PFO is pathogenic or incidental.26

A hypercoagulable state may increase the risk of venous thrombosis and paradoxical embolism in patients with PFO, and coagulation disorders are common in patients with cryptogenic stroke and PFO.27,28 Atherosclerosis is an alternative etiological factor. PFO is associated with less atherosclerosis in patients aged 55 years or younger with cryptogenic TIA/stroke compared with controls without arterial cerebrovascular events.29 However, some young patients may still have incidental PFO, especially those in the upper age category, with conventional stroke risk factors and/or with low-risk PFO features on TEE. Some older patients may have pathogenic PFO, especially those without conventional stroke risk factors and/or with high-risk PFO features.26 A careful assessment of risk factors and an extensive imaging protocol for atherosclerosis is mandatory for patients with PFO.

Diagnosis of Paradoxical Embolism

A stroke is cryptogenic and possibly related to a PFO when brain imaging shows an embolic ischemic lesion and a definite cause cannot be established after extracranial and intracranial vascular imaging, TCD ultrasound with emboli monitoring, TEE, Holter monitoring, and coagulopathy screening. Many published studies have failed to include a complete set of investigations, and the diagnostic methods vary, resulting in heterogeneity between studies and results that are difficult to interpret.19,30

A patient with cryptogenic stroke may refer to periods of inactivity or immobility during the weeks before the event, facilitating venous thrombus formation. The patient may also indicate activities associated with a Valsalva maneuver immediately before stroke onset, promoting increased RLS.31 Cryptogenic ischemic stroke on waking in patients with sleep apnea may also be due to paradoxical embolism.32 Therefore, a careful case history may support a diagnosis of paradoxical embolism.

A venous thrombosis may be difficult to find.33 Autopsy studies have documented pelvic vein or inferior vena cava thrombus in 22% of patients with paradoxical emboli.34 Results from series with clinical examination, ultrasound venography, and MR venography vary enormously.33-36 If a venous thrombosis is found, the diagnosis of paradoxical embolism is strengthened. However, insisting upon evident deep vein thrombosis for the diagnosis of cryptogenic stroke will inevitably lead to underdiagnosis, as screening for deep vein thrombosis fails to uncover many venous sources.31

PFO and Recurrent Cerebrovascular Events

For a patient with cryptogenic stroke, preventing further damage to the brain is of paramount importance. Given the uncertainty of a TIA diagnosis, inclusion of TIA may confound the diagnosis and the issue of secondary prevention. The estimate for recurrent ischemic stroke, whether clinical symptoms are transient or permanent, is the one item of prognostic interest.
Case-control studies of patients with cryptogenic stroke indicate an association between PFO and recurrent stroke/TIA. After an initial cryptogenic stroke, the risk of recurrent stroke is claimed to be modestly increased with medical treatment alone.37 However, a recent meta-analysis of observational studies of medically treated patients with PFO does not support an increased relative risk of recurrent ischemic events in those with a PFO or without a PFO.30 The high degree of heterogeneity among studies indicates that differences in patient characteristics and diagnostic procedures have likely influenced outcome rates and that any nonrandomized data should be viewed with extreme caution.

Medical Treatment After Cryptogenic Stroke With PFO
Because anticoagulation is more efficacious than antiplatelet therapy in treating venous thrombosis, long-term anticoagulation has also been recommended for treating cryptogenic stroke, but data supporting this view have been weak. The only randomized treatment data come from the PFO in Cryptogenic Stroke Study (PICSS), which compared warfarin with aspirin.38 In patients with cryptogenic stroke and PFO, event rates were 9.5% with warfarin and 17.9% with aspirin; however, this difference did not reach statistical significance ($P = .28$). In patients with clearly embolic infarcts, event rates were 6.8% with warfarin and 18.8% with aspirin ($P = .03$). Although the PICSS data are claimed to support equivalence between aspirin and warfarin, results should be interpreted with caution.26,27 Warfarin seems biologically reasonable, and a substantial protective effect of warfarin cannot be excluded.

PFO Closure After Cryptogenic Stroke
PFOs are repairable lesions, and percutaneous closure is an intuitively attractive mechanical solution for stroke prevention. Meta-analysis of different treatment series have shown that warfarin is associated with fewer neurological events than antiplatelet treatment, but is comparable to PFO closure, and that transcatheter closure of PFOs is associated with a decreased risk of recurrent stroke and TIA.39,40 Yet, the discussion remains open.41-44

The efficacy of PFO closure in preventing recurrent ischemic events is being tested in at least three major randomized trials. The CLOSURE I trial completed patient follow-up in 2010. The trial failed to meet its primary endpoint of stroke or TIA, although preliminary results suggest a small but statistically insignificant benefit of device closure over the current best medical therapy. The full results will be presented later in 2010. The RESPECT trial and the PC trial in Europe will be completed in 2011. The French CLOSE trial is still recruiting. The Gore REDUCE clinical study is a multinational trial with an estimated completion date of 2015. These trials will likely help resolve the open debate about whether PFO closure is a viable option for treating cryptogenic stroke/TIA patients as compared to medical treatment alone.

PFO AND MIGRAINE
Observational studies indicate an increased prevalence of PFO in migraine with aura compared with migraine without aura or healthy controls, as well as an increased prevalence of migraine in persons with PFO.45 This apparent association between migraine and PFO was, however, not found in a recent large case-control study and in a population-based cohort study.46,47 Although there are many feasible mechanisms supporting an association between PFO and migraine with aura, current evidence is insufficient to support a causal relationship.48

A large number of publications supports an association between migraine with aura and ischemic stroke. The mechanisms by which migraine can lead to stroke are several and the association between the two diseases is complex.49,50 Microemboli through a PFO is but one mechanism. Future studies should aim to identify relevant mechanisms and which individuals with migraine are at greatest risk for ischemic stroke.

PFO closure may dramatically improve migraine with aura. This is consistently found in a large number of uncontrolled observational studies. The only large randomized trial failed to support such a conclusion.51 This trial missed a significant effect for primary or secondary endpoints, but the exploratory analysis was encouraging. Several randomized, controlled, double-blinded studies are now underway that may firmly establish the role of PFO closure in persons suffering from migraine.52

CONCLUSION
As seen from the brain, PFO still looks like a serious threat to neurologic health. Although a vast amount of data exist, we still cannot see who is at high risk and who is at low risk, nor can we see which PFO is incidental and which is pathogenic. We need to be more accurate in our efforts, and it is imperative to clarify the question of PFO closure versus no closure by randomizing patients to ongoing long-term studies. If we can do that, we may be able to close a long-lasting hole in our knowledge.

Lars Thomassen, MD, PhD, is a professor in the Department of Neurology, Center for Neurovascular Diseases, Haukeland University Hospital in Bergen, Norway. He has disclosed that he hold no financial interest in any
product or manufacturer mentioned herein. Dr. Thomassen may be reached at +47 55 97 50 00; ltho@haukeland.no.

Ulrike Waje-Andreasen, MD, PhD, is a senior neurologist in the Department of Neurology, Center for Neurovascular Diseases, Haukeland University Hospital in Bergen, Norway. He has disclosed that he hold no financial interest in any product or manufacturer mentioned herein.


