Clinical and Imaging Findings in Cryptogenic Stroke Patients With and Without Patent Foramen Ovale

The PFO-ASA Study

C. Lamy, MD; C. Giannesini, MD; M. Zuber, MD; C. Arquizan, MD; J.F. Meder, MD; D. Trystram, MD; J. Coste, PhD; J.L. Mas, MD; for the Patent Foramen Ovale and Atrial Septal Aneurysm Study Group

Background and Purpose—Patent foramen ovale (PFO) has been identified as a potential risk factor for stroke, but the mechanisms of PFO-associated stroke remain unsettled. The aim of our study was to evaluate possible differences in stroke risk factors and stroke patterns between patients with and without PFO that may give clues to the mechanism of PFO-associated stroke.

Methods—This prospective, multicentric study involved 581 young cryptogenic stroke patients. The presence of PFO and atrial septal aneurysm was assessed by transesophageal echocardiography and reviewed independently by 2 experienced sonographers. Clinical, brain, and vascular imaging findings were reviewed by 2 neurologists and 2 neuroradiologists.

Results—Of the 581 stroke patients, 267 (45.9%) had PFO. Patients with PFO were younger (OR, 0.95; 95% CI, 0.93 to 0.97) and less likely to have traditional risk factors such as hypertension (OR, 0.49; 95% CI, 0.28 to 0.85), hypercholesterolemia (OR, 0.56; 95% CI, 0.34 to 0.93), or current smoking (OR, 0.67; 95% CI, 0.47 to 0.97). Features suggestive of paradoxical embolism, such as Valsalva-provoking activities or deep vein thrombosis, were not more frequent in patients with PFO. Migraine was more common in patients with PFO (27.3%) than in those without PFO (14.0%). PFO (OR, 1.75; 95% CI, 1.08 to 2.82), particularly when associated with atrial septal aneurysm (OR, 2.71; 95% CI, 1.36 to 5.41), was significantly associated with migraine after adjustment for age and sex.

Conclusions—Differences in stroke risk factors and stroke patterns suggest that different stroke mechanisms occur in patients with and without PFO. PFO is significantly and independently associated with migraine, and this association is even stronger in patients with PFO and atrial septal aneurysm. (Stroke. 2002;33:706-711.)

Key Words: embolism, paradoxical ▪ heart septal defects, atrial ▪ patent foramen ovale ▪ stroke

Patent foramen ovale (PFO) and atrial septal aneurysm (ASA) have been identified as potential risk factors for stroke. In a recent meta-analysis of case-control studies comparing patients <55 years of age with ischemic stroke with nonstroke control subjects, ORs of stroke were 3.1 (95% CI, 2.3 to 4.2) for PFO and 6.1 (95% CI, 2.5 to 15.2) for ASA. Whether the relationship between PFO and stroke is causal and, if so, the precise stroke mechanism are still a matter of debate. Potential mechanisms include paradoxical embolism from a venous source, direct embolization from thrombi formed within the PFO or an associated ASA, and thrombus formation caused by atrial arrhythmias, such as paroxysmal atrial fibrillation.

The aim of the study was to assess stroke risk factors and stroke patterns in cryptogenic stroke patients with and without PFO to provide clues to PFO-associated stroke mechanism.
TABLE 1. Risk Factors for Stroke in Patients With and Without PFO

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No PFO (n=314)</th>
<th>PFO (n=267)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean), y</td>
<td>44.5</td>
<td>40.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>62.1</td>
<td>52.1</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Risk factors, %

| Hypertension*                      | 21.3           | 8.6         | <0.0001 |
| Diabetes mellitus*                 | 5.1            | 3.0         | 0.2    |
| Hypercholesterolemia*              | 23.2           | 10.9        | <0.0001 |
| Current smoking                    | 51.6           | 43.4        | 0.05   |
| Alcohol†                           | 21.3           | 13.1        | 0.01   |
| Current use of oral contraceptives | 40.3           | 51.6        | 0.08   |
| Body mass index >27 kg/m²          | 29.0           | 18.5        | 0.003  |
| Prior stroke                       | 3.2            | 2.2         | 0.5    |

n=581.

*Known before stroke.
†More than 3 standard drinks per day during the previous month.

Catheter angiography (n=360; within 2 weeks after stroke onset in 83.2% of cases), magnetic resonance angiography (n=220), or cervical and transcranial ultrasonography (n=495). The decisions to perform additional investigations and to search for latent deep vein thrombosis or pulmonary embolism in patients with PFO were left to the investigator in charge of the patient. In 10 centers, 24-hour ECG recording was performed systematically in all patients (n=173, 84 with PFO) between days 7 and 21 after stroke onset. Twenty-four-hour ECG monitoring was performed after the acute phase of stroke to exclude arrhythmias secondary to stroke. Criteria derived from the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification17 were used to rule out definite causes of stroke.16

The clinical and imaging data of all patients were collected by the coordinating center and reviewed by 2 neurologists and 2 neuroradiologists who were blinded to the results of transesophageal echocardiography regarding the presence of PFO and ASA. Cases with potential violation of inclusion criteria were submitted to the Validation Committee.

Clinical Data

The following information was systematically recorded: (1) baseline characteristics and traditional risk factors of stroke (Table 1); (2) past vascular events, such as stroke, deep venous thrombosis, or pulmonary embolism; (3) history of migraine according to International Headache Society criteria16; (4) stroke severity assessed on a modified Rankin scale19 at the time of inclusion; (5) palpitations preceding or accompanying stroke onset; (6) neurological features reported as suggestive of cardiogenic embolism,20,21 such as abrupt, nonprogressive onset defined as no deficit on waking from sleep, peak deficit within the first 10 minutes, no subsequent deterioration during the first 24 hours, diminished level of consciousness at onset, cortical deficits, including Wernicke’s aphasia, isolated hemianopsia, hemineglect, and apraxia; and (7) features suggesting paradoxical embolism, such as the presence of deep venous thrombosis or pulmonary embolism, Valsalva-provoking activity within the 30 minutes preceding stroke onset (sporting effort, straining at stool, intercourse, lifting a heavy weight, getting up, laughing, and coughing);8 and circumstances predisposing to deep venous thrombosis before stroke onset, such as immobilization, anesthesia, surgery, or pregnancy.22

Brain and Vascular Imaging Findings

The following brain and vascular imaging features were analyzed: (1) stroke arterial territory following previously published templates23-25; (2) imaging features of previous stroke; and (3) neuroimaging data suggestive of cardiogenic embolism,20,26-28 such as hemorrhagic infarct on neuroimaging performed within 2 weeks of stroke onset,29 superficial infarct, infarct larger than one half of the cerebral hemisphere, involvement of specific (Table 2) or multiple arterial territories, and the presence of intracranial occlusion on catheter angiography.

Echocardiography

The presence of PFO and ASA was assessed by transesophageal echocardiography with a contrast study performed at rest and during provocative maneuvers (Valsalva and cough test) by use of 5-MHz multipeaks (86.4%) and biplane (13.6%) transducers. Examinations were recorded on super VHS videotapes and independently reviewed by 2 experienced sonographers.16

The contrast study was considered positive if ≥3 microbubbles appeared in the left atrium, either spontaneously or after provocative maneuvers, within 3 cardiac cycles after complete opacification of the right atrium. The degree of shunting was defined as small (3 to 9 microbubbles), moderate (10 to 30 microbubbles), or large (>30 microbubbles). ASA was diagnosed when the atrial septum exhibited an excursion into the left or right atrium or both of ≥11 mm.

The 2 sonographers disagreed on the presence or absence of PFO in 13.9% of cases, the presence or absence of ASA in 6.6%, the degree of shunt in 26.5%, and the size of ASA in 8.4% of cases. Disagreements were resolved by unblinded consensus review.

Statistical Analysis

Clinical data, brain, and vascular imaging findings were compared between patients with and without PFO and between patients with small to moderate and those with large PFO. Comparisons between groups were performed by a χ² test, Fisher’s exact test, or t test for
unpaired data whenever applicable. Factors independently associated with PFO were identified by logistic regression analysis. ORs with 95% CIs were calculated.

The association between migraine and PFO was examined through logistic regression analysis with migraine as a dependent variable and age, sex, PFO, and ASA as independent variables. To assess the role of PFO and ASA in isolation from or in association with each other, we used an independent variable divided into 4 categories: no PFO or ASA, isolated PFO, isolated ASA, and PFO and ASA.

Results
This study included 581 consecutive patients. Of these, 267 patients (45.9%) had PFO and 61 (10.5%) had ASA. Of the 267 patients with PFO, 48% had small to moderate shunts and 52% had large shunts. PFO was strongly associated with ASA: 51 of the 267 patients with PFO (19.1%) also had ASA compared with 10 of 314 of those without PFO (3.2%; P<0.0001). The prevalence of ASA increased with the degree of shunt: 4.4%, 12.5%, and 25% in patients with small, moderate, and large shunts, respectively (P<0.0001).

Patients Characteristics and Stroke Patterns
Baseline characteristics and risk factors of stroke, according to the presence of a PFO, are shown in Table 1. Patients with PFO were younger and less likely to have traditional risk factors of stroke than those with no PFO. In logistic regression analysis (with age, sex, stroke risk factors, and ASA as independent variables), age (OR, 0.95; 95% CI, 0.93 to 0.97), hypertension (OR, 0.49; 95% CI, 0.28 to 0.85), hypercholesterolemia (OR, 0.56; 95% CI, 0.34 to 0.93), and current smoking (OR, 0.67; 95% CI, 0.47 to 0.97) were inversely associated with PFO, whereas ASA (OR, 7.4; 95% CI, 3.6 to 15.2) was positively associated with PFO.

Table 2 shows the characteristics of stroke. Patients with PFO had on average a less severe stroke as assessed by the Rankin scale at the time of inclusion, and this remained significant after adjustment for age, sex, vascular risk factors, and presence of ASA (P=0.01). Overall, no difference was found regarding arterial territories. Neuroimaging features of previous stroke were less frequent in patients with PFO, but this association was not significant after adjustment for age and risk factors for stroke. No significant difference was found between small to moderate and large shunts in terms of patient and stroke characteristics.

Mechanism of PFO-Associated Stroke
Clinical and imaging features suggestive of cardiogenic embolism did not differ significantly between groups, except for a higher frequency of cortical signs and of infarcts in the superior cerebellar artery territory in the PFO group. Features consistent with the diagnosis of paradoxical embolism were not found more frequently in patients with PFO than in patients without PFO, except for a higher frequency of circumstances predisposing to deep venous thrombosis (Table 3). Features suggesting cardioembolism or paradoxical embolism were not associated with the degree of shunt.

Of the 267 patients with PFO, 122 (45.7%) had a search for latent deep venous thrombosis or pulmonary embolism within 4 weeks after stroke onset (43% within 8 days). Investigations consisted of Doppler ultrasonography (n=112), phlebography (n=3), and pulmonary scintigraphy (n=43). A latent deep venous thrombosis or pulmonary embolism was found in 5 patients (4.1%) 4 to 12 days after stroke onset.

Discussion
This is the first prospective, multicentric study comparing stroke risk factors and stroke patterns in a large population of young cryptogenic stroke patients with or without PFO. We selected patients ≤55 years of age because the higher prevalence of large-vessel atherosclerosis or small-artery disease in the elderly makes the diagnosis of cryptogenic stroke less frequent than in the young. In addition, the association of PFO and cryptogenic stroke has been consistently reported in this age group, whereas this association in those >55 years of age remains unconfirmed.6 Independent

**TABLE 3. Arguments Suggesting Paradoxical Embolism**

<table>
<thead>
<tr>
<th></th>
<th>No PFO, %</th>
<th>PFO, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=314)</td>
<td>(n=267)</td>
<td></td>
</tr>
<tr>
<td>Valsalva-provoking activity within 30 min preceding stroke onset*</td>
<td>8.9</td>
<td>13.5</td>
<td>0.2</td>
</tr>
<tr>
<td>History of DVT or pulmonary embolism</td>
<td>2.5</td>
<td>1.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Circumstances predisposing to DVT before stroke onset†</td>
<td>1.6</td>
<td>4.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Patient DVT or pulmonary embolism</td>
<td>0</td>
<td>0.7</td>
<td>0.2</td>
</tr>
</tbody>
</table>

DVT indicates deep vein thrombosis. n=581.
*Sporting effort, straining at stool, intercourse, lifting a heavy weight, getting up, laughing, and coughing.
†Immobilization, anesthesia, surgery, and pregnancy.

**TABLE 4. Association Between Migraine, PFO, and ASA as given by Logistic Regression Analysis**

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>0.96</td>
<td>0.94–0.98</td>
<td>0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>2.8</td>
<td>1.77–4.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Septal abnormality</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No PFO, no ASA (n=304) 1
PFO, no ASA (n=216) 1.75 1.08–2.82 0.02
ASA, no PFO (n=10) 3.38 0.80–14.21 0.09
PFO and ASA (n=51) 2.71 1.36–5.41 0.005
review of transesophageal echocardiography examinations by 2 experienced sonographers provided prevalences of PFO and ASA that were in the range of reported rates. To minimize information biases, clinical and imaging data were reviewed by 2 neurologists and 2 neuroradiologists who were blinded to the presence of PFO.

The first finding of our study is that cryptogenic stroke patients with PFO were younger and less likely to have traditional risk factors for stroke than patients without PFO. They also had on average a less severe stroke. These differences in stroke risk factors and stroke severity have not been stressed previously and suggest different stroke mechanisms in patients with and without PFO.

Some features suggestive of cardiogenic embolism were more frequent in the PFO group, which also suggests different stroke mechanisms in patients with and without PFO. These features, however, have a limited positive or negative predictive value for the diagnosis of cardioembolism. In contrast to the study by Steiner et al., we did not find embolic features to be more common in patients with large shunts than in patients with small to moderate shunts. On the whole, features suggesting paradoxical embolism were not more frequent in patients with PFO than in those without PFO, suggesting that paradoxical embolism might not be the prevalent mechanism of PFO-associated stroke, a finding consistent with our previous experience. These features, however, may be insufficient or inaccurate and therefore not useful in clinical practice. In the present study, investigators were not blinded to the presence of PFO when recording features suggesting paradoxical embolism. However, if this unblinded recording had introduced a bias, a higher prevalence of these features in patients with PFO would have been expected. The frequency of latent deep venous thrombosis in stroke patients with PFO was not an objective of our study, and the search for deep venous thrombosis was left to the investigator in charge of the patient. It was performed in fewer than half of the patients with PFO by use of various diagnostic techniques. This low rate of search for deep venous thrombosis suggests that many investigators either are not convinced that paradoxical embolism is a prevalent mechanism of PFO-associated stroke or are concerned about the low yield and pitfalls of a systematic search for deep venous thrombosis. Indeed, the source of emboli may remain undetected because of its location or the size of the thrombus. Venous thrombi may disappear either spontaneously or after anticoagulation before investigations are performed. Finally, venous thrombosis may be a mere consequence of immobilization resulting from stroke rather than a cause of stroke. The low rate of latent deep venous thrombosis found in the present study is consistent with the result of our previous study in young stroke patients. The role of a hypercoagulable state in the pathophysiology of PFO-associated stroke cannot be evaluated from this study because patients with a definite coagulopathy were not included in the study.

Our study does not provide argument for transient arrhythmia as a mechanism of PFO-associated stroke. Palpitations preceding or accompanying stroke onset were rare, and 24-hour ECG recording did not reveal embolicogenic arrhythmias. It should be stressed, however, that arrhythmias are often clinically silent and that a single 24-hour Holter monitoring is not the optimal method to detect potentially more spaced-out episodes of transient arrhythmias.

Another interesting finding of our study is that migraine was more common in cryptogenic stroke patients with PFO (27.3%) than in those without PFO (14.0%). This result is consistent with recent studies in stroke patients and nonstroke individuals that showed an association between migraine with aura and PFO as detected by transcranial Doppler or transthoracic echocardiography. At the time of the present study, the relation between migraine with aura and PFO had not emerged in the literature. Therefore, investigators were not asked to differentiate migraine with and without aura and were not blinded to the presence of PFO. However, because investigators were not aware of a potential relation between migraine and PFO, an information bias seems unlikely. The present study is the first to confirm the association between PFO and migraine with contrast transesophageal echocardiography as the diagnostic procedure with independent review of transesophageal echocardiographies by 2 sonographers who were blinded to the presence of migraine. In addition, our study, based on a large population of young stroke patients, shows that PFO is independently associated with migraine and that this association is stronger when PFO is associated with ASA. We did not find an increasing prevalence of migraine with the degree of shunt. No statistically significant association was found between migraine and isolated ASA, but the number of patients with isolated ASA was small. The link between migraine, PFO, and ASA is unclear. A particular genetic substrate might determine both atrial septal abnormalities and migraine. Another hypothesis, recently suggested by Wilmshurst et al., is that PFO might allow trigger substances of migraine (such as vasoactive chemicals) in the venous blood to bypass the pulmonary filter and to reach the systemic circulation in amounts large enough to induce a migraine attack. Further studies are needed to elucidate the relationships between migraine and atrial septal abnormalities.

Appendix

Coordinating Center
J.L. Mas, C. Arquizan, C. Lamy, M. Zuber, C. Gianesini, D. Trystram, and J.F. Méder, Sainte-Anne Hospital, Paris, France.

Scientific Committee

TEE Committee

Validation Committee

Participating Institutions and Investigators

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References


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