Patent Foramen Ovale May Be Causal for the First Stroke but Unrelated to Subsequent Ischemic Events

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Background and Purpose—Studies with very long follow-up are scarce in patients with cryptogenic stroke and patent foramen ovale (PFO). Little is known about the etiology of recurrent cerebrovascular events (CVE) in PFO patients.

Methods—We collected information on recurrent CVE in 308 patients with cryptogenic stroke and PFO and sought to determine concurrent stroke causes that had emerged or been newly detected since the index event. One hundred fifty-eight patients received aspirin (48%), clopidogrel (2%), or oral anticoagulants (50%; medical group). One hundred fifty patients underwent percutaneous PFO closure (closure group).

Results—Mean age at index event was 50 years (SD 13). In 33% of patients, the index stroke or transient ischemic attack was preceded by at least 1 CVE. Mean follow-up was 8.7 ± 4.0 years. During follow-up, 32 recurrent CVE (13 strokes and 19 transient ischemic attacks) occurred in the medical and 16 recurrent CVE (8 strokes and 8 transient ischemic attacks) in the closure group. Concurrent etiologies were identified for 12 recurrent CVE in the medical group (38%): large artery disease (9%), small artery disease (6%), cardioembolism (13%), cerebral vasculitis (3%), and antiphospholipid-antibody-syndrome (6%). In the closure group, 7 recurrent CVE had a concurrent etiology (44%): large artery disease (6%), small artery disease (19%), cardioembolism (13%), and thrombophilic disorder (6%). The frequency of concurrent etiologies did not differ between patients with recurrent CVE under medical treatment and those undergoing PFO closure (P = 0.68).

Conclusions—Concurrent etiologies are identified for more than one third of recurrent ischemic events in patients with cryptogenic stroke, casting doubt on the sole causal role of PFO. (Stroke. 2011;42:00-00.)

Key Words: patent foramen ovale ▪ right-to-left shunt ▪ cryptogenic stroke ▪ recurrence rate

Studies with very long follow-up in patients with cryptogenic stroke and patent foramen ovale (PFO) are scarce. A recent meta-analysis of 15 observational studies assessed the risk of stroke recurrence under antithrombotic treatment.1 The follow-up ranged from 1.8 to 5.3 years. There are only a few large studies reporting midterm results after percutaneous PFO closure.2–4

Given that competing stroke etiologies are likely to emerge or to be newly diagnosed with advancing age, longer follow-up duration may shed more light on the causal link between PFO and recurrent ischemic events. For instance, a PFO that had been responsible for the initial stroke may prove unrelated to subsequent events if a diagnostic reinvestigation identifies a more likely cause of stroke. In addition, reinvestigation might identify a cause of stroke that had been missed with the first event.

In 2004, we reported recurrence rates in patients with PFO and otherwise-unexplained ischemic stroke after a mean follow-up of 2.3 years.5 The present study extends the same series to a mean follow-up of 8.7 years. In patients with recurrent ischemic events, we sought to identify concurrent stroke causes that had emerged since the index event.

Materials and Methods

Patients

The selection criteria for this study have been described previously.6 In brief, we identified all patients with ischemic stroke, transient ischemic attack (TIA), or transient monocular blindness who were admitted to our stroke center from January 1994 to August 2000. Ischemic stroke and TIA were diagnosed by a neurologist. The diagnosis of ischemic stroke was based on a focal neurological deficit that lasted 24 hours or longer with corresponding findings on computed tomography or magnetic resonance imaging.6 A TIA was defined as a focal neurological deficit that resolved completely within 24 hours. All patients underwent routine blood analysis, color-coded duplex ultrasound of the extra- and intracranial arteries, 24-hour echocardiogram and transesophageal echocardiography. Ad-
dential diagnostic workup was left to the discretion of the treating physician and included computed tomography— or magnetic resonance— angiography, laboratory screening for cerebral vasculitis, or thrombophilia. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria were used to classify the etiology of stroke. A cryptogenic stroke was defined as brain infarction that is not attributable to definite cardioembolism, large artery atherosclerosis, small artery disease, or other determined etiology.

Three hundred eight patients had a PFO and no other definite cause of stroke (cryptogenic stroke). One hundred fifty-eight patients were treated with either oral anticoagulants or antplatelets according to the discretion of the attending neurologist (medical group). Oral anticoagulants were adjusted to a target international normalized ratio of 2.0 to 3.0, aspirin was prescribed at a mean dose of 233 mg/d, and clopidogrel was prescribed at a dose of 75 mg. The remaining 150 patients underwent percutaneous PFO closure (PFO closure group).5

Transesophageal Echocardiography and Diagnosis of PFO
A right-to-left shunt was diagnosed if at least 1 microbubble appeared early in the left atrium either spontaneously or after provocative maneuvers. The degree of shunting was defined as small if 1 to 5 microbubbles occurred, moderate if 6 to 20 bubbles occurred, and large if >20 bubbles occurred. An atrial septal aneurysm was diagnosed when the interatrial septum was abnormally flaccid with an excursion of ≥10 mm into the right or left atrium and base span of at least 15 mm.8

Bleeding Complications
Bleeding complications were classified according to the Global Strategies for Opening Occluded Coronary Arteries (GUSTO) criteria.9 Severe or life-threatening bleeding was defined as substantial bleeding that caused hemodynamic compromise and required intervention. Moderate bleeding complication was assumed when bleeding required blood transfusion, but did not result in hemodynamic compromise. Moderate bleeding complications and severe life-threatening bleeding were assessed and defined as major bleeding. Symptomatic intracerebral hemorrhages were analyzed separately.

Risk Factors
We assessed the following risk factors: hypertension (treated hypertension or systolic blood pressure >140 mm Hg and diastolic blood pressure >90 mm Hg measured on 2 different occasions), diabetes mellitus (symptoms of diabetes plus random blood glucose concentration >11 mmol/L or fasting glucose >7 mmol/L), current cigarette smoking, total cholesterol (total venous plasma cholesterol concentration >5 mmol/dL), and obesity (body mass index >25 kg/m²).

Follow-Up
We contacted all patients, their family physicians, or both to request information concerning recurrent ischemic stroke or TIA, antithrombotic treatment, and PFO closure since the completion of our previous study, using structured telephone interviews and written surveys.5 In case of suspicion of a recurrent event, we collected all available medical records related to the event. A neurologist ascertained all recurrent strokes and TIAs based on the same criteria as for diagnosis of the index event. Finally, we reviewed results of the diagnostic workup that had been performed to identify etiology of the recurrent event.

Follow-up information was available for all 308 patients at some point in time. During follow-up, 2 patients on medical treatment subsequently underwent surgical closure and 12 patients underwent endovascular closure of the PFO. These patients were included in our analysis for the time they were treated medically. The reasons for PFO closure were unwillingness to continue lifelong antithrombotic treatment or patient's belief that PFO closure offers better stroke prevention. None of the patients had experienced a recurrent event before the procedure.

| Table. Baseline Clinical and Demographic Characteristics of 158 Patients With PFO Under Medical Treatment and 150 Patients With PFO With PFO Closure |
|-------------------------------------------------|-----------------|-----------------|-----|
| Characteristic                                   | Medical Treatment (N = 158) | PFO Closure (N = 150) | P  |
| Mean age, y/SD                                   | 51/13           | 50/12           | NS  |
| Female sex, n/%                                  | 66/42           | 70/47           | NS  |
| Follow-up, y/SD                                  | 8.1/4.7         | 9.2/3.0         | NS  |
| Index event, n/%                                 | 40/25           | 53/35           | NS  |
| Transient ischemic attack                        | 118/75          | 97/65           | NS  |
| Stroke                                           | 44/29           | 59/39           | 0.03|
| Previous cerebrovascular event                   |                 |                 |     |
| Cardiovascular risk factor, n/%                  |                 |                 |     |
| Arterial hypertension                            | 50/32           | 42/28           | NS  |
| Diabetes mellitus                                | 14/9            | 6/4             | NS  |
| Smoking                                          | 51/33           | 49/33           | NS  |
| Total cholesterol (mmol/dL)                      | 5.8±1.3         | 5.5±1.2         | NS  |
| BMI >25                                          | 73/46           | 65/43           | NS  |
| Atrial septal anatomy                            | 123/78          | 113/75          | NS  |
| PFO only                                         | 35/22           | 37/25           | NS  |
| Large RLS                                        | 97/61           | 119/80          | 0.001|

PFO indicates patient foramen ovale; BMI, body mass index; ASA, atrial septal aneurysm; RLS, right-to-left shunt; SD, standard deviation.

Statistics
Continuous variables are expressed as mean ± SD. The χ² test for contingency tables was used to compare nominal variables. Statistically significant was assumed at a probability value <0.05.

Results
Baseline Characteristics
Demographic data and baseline clinical and echocardiographic characteristics are summarized in the Table.

The medical and closure group did not differ in terms of age, sex, vascular risk factors, type of index event, and frequency of coinciding atrial septal aneurysm.

Patients undergoing PFO closure had a larger right-to-left shunt (P <0.001) and were more likely to have suffered more than 1 cerebrovascular event (CVE; P <0.03).5

Medical Treatment and Bleeding Complications
Seventy-nine patients (50%) received antplatelets immediately after the index event. Of them, 2 patients were treated with clopidogrel, and the remaining patients were given aspirin at a mean dose of 233 mg/d. Seventy-nine patients (50%) received oral anticoagulants with a target international normalized ratio of 2.0 to 3.0.

By the end of follow-up, 10 patients (6.3%) had discontinued antithrombotic treatment. The proportion of patients still on anticoagulants declined from 50% to 35%, while the proportion of patients on antplatelets increased from 50% to 58%.

In the medical group, there were 2 major bleeding complications (1.3%) in patients with anticoagulants and 1 major bleeding (0.6%) in patients on antplatelets. Two patients
(1.3%) suffered a symptomatic intracerebral bleeding. Both patients were treated with anticoagulants. There was no significant difference between the treatment regimens concerning bleeding complications.

In the PFO closure group, a major bleeding occurred in 1 patient (0.7%). One patient (0.7%) suffered an intracerebral bleeding.

**PFO Closure**

Percutaneous PFO closure was successful in 148 patients (99%) and failed in 2 patients. Complete PFO closure as assessed by transesophageal echocardiography at 6 months was achieved in 83%, whereas a small, moderate, or large shunt persisted in 10%, 3%, or 4% of patients, respectively. Etiology of Recurrent Stroke and TIA

Medical Group

During a mean follow-up of 8.1±4.7 years, 13 recurrent strokes and 19 recurrent TIAs occurred in 32 patients (20.3%). Sixteen patients (10.1%) died. There were 5 cardiovascular deaths and 11 deaths unrelated to cardiovascular events. Six strokes and 11 TIA occurred in patients treated with antiplatelets; 7 strokes and 8 TIAs occurred in patients receiving anticoagulants. The frequency of recurrent stroke or TIA did not differ with respect to treatment with antiplatelets or anticoagulants (P=0.83 for stroke and P=0.41 for TIA).

The repeated etiologic workup was individually tailored, taking into consideration the time elapsed from the previous diagnostic evaluation. Concurrent causes of stroke or TIA, conventionally considered more likely than PFO, were found in 12 patients (38%). Four patients (13%) had atrial fibrillation, 3 patients (9%) had large artery disease, 2 patients (6%) had small artery disease, 2 patients (6%) had antiphospholipid-antibody syndrome, and 1 patient (3%) had cerebral vasculitis (Figure A).

Twenty patients (63%) did not show any concurrent cause. Of them, 4 patients (20%) underwent a complete etiologic workup; the diagnostic re-evaluation of the remaining 16 patients (80%) consisted of ancillary examinations deemed appropriate by the treating physicians.

Among patients with recurrent stroke or TIA, concurrent etiologies were more frequent in those older than age 55 years at the time of the index event than in younger patients (P=0.018). Patients with or without concurrent causes for the recurrent event did not differ in terms of vascular risk factors, completeness of initial work-up, or delay between index and recurrent event. Atrial septal aneurysm and large right-to-left shunt were equally prevalent among patients with and without concurrent causes of the recurrent event.

**PFO Closure Group**

During a mean follow-up of 9.2±3.0 years, 16 recurrent cerebrovascular events (10.7%; 8 strokes and 8 TIAs) occurred in the PFO closure group. There were 7 fatalities (4.7%) during follow up: 4 cardiovascular and 3 noncardiovascular deaths.

Seven recurrent cerebrovascular events (44%) had a concurrent etiology: 1 patient (6%) had large artery disease, 3

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**Figure A.** Etiologies of 32 recurrent cerebrovascular events in 158 medically treated PFO patients. **B.** Etiologies of 16 recurrent cerebrovascular events in 150 PFO patients with PFO closure.
patients (19%) had small artery disease, 2 patients (13%) had atrial fibrillation, and 1 patient (6%) had increased thrombin-antithrombin III complex and heparin cofactor II deficiency (Figure B). Of the remaining 9 patients (56%) with cerebrovascular recurrence, 2 patients (13%) had a relevant residual right-to-left shunt, whereas the recurrent event was still defined as cryptogenic in the other 7 patients (44%).

Patients with or without concurrent causes for the recurrent event did not differ in terms of age, delay between the index and the recurrent event, coexistence of an atrial septal aneurysm, size of right-to-left shunt, or presence of residual shunt after closure. Among patients with recurrent events, hypercholesterolemia was more frequent in patients with concurrent causes than in those without (100% versus 56%; \( P=0.042 \)).

The frequency of concurrent etiology did not differ between patients with recurrent CVE under medical treatment and those undergoing PFO closure (\( P=0.68 \)).

**Discussion**

The aim of this study was to assess the role of concurrent stroke etiologies that may emerge or become evident during very-long-term follow-up. We followed 308 consecutive patients for a mean period of 8.7 years, which was substantially longer than has been the follow-up of previous studies.1–4

Several case-control studies implicated PFO as a potential cause of stroke, presumably because of paradoxical embolism.1,10 This observational evidence and the continuous improvement of catheter-driven closure devices has led to widespread use of percutaneous device closure of the PFO.

To date, the concept that closing the PFO would reduce risk of recurrent stroke, although appearing straightforward, has not been proven. The only randomized controlled trial reported so far did not observe any difference between medical treatment and PFO closure in preventing recurrent stroke or TIA.11 The reasons behind the lack of difference remain to be analyzed, though low recurrence rates in both treatment arms are no doubt a major challenge for this and for future trials.

To date, other studies reported only recurrence rates, but not the etiologies of recurrent events. In the present study, we use a different approach to assess the role of PFO closure and medical treatment in secondary prevention of PFO-related stroke. If closing a PFO is an effective preventive measure, not only just the risk of recurrent stroke will drop, but also the proportion of cryptogenic recurrent events will decline, giving rise to concurrent stroke etiologies. Conversely, if concurrent etiologies are prevalent in a significant proportion of patients with recurrent stroke or TIA, discontinuation of antithrombotic treatment after PFO closure is not justified.

If case-control studies indicate an OR 3.32 of finding a PFO in stroke of undetermined etiology compared with strokes of determined etiology, the odds that another etiology than the PFO is responsible for the stroke can be calculated by the inverse of OR, ie, 1/OR = 1/3.32 = 30%.12

In the present study, 38% of recurrent CVE in medically treated patients had a concurrent condition that was considered a more probable etiology than was the PFO. This rate is likely to be underestimated, as 50% of the patients with a recurrent event did not have a complete etiologic re-evaluation. Similarly, concurrent etiologies for recurrent stroke or TIA were diagnosed in 44% of patients undergoing PFO closure; this is a rate that is slightly higher, however below statistical significance. It appears that closing the PFO has no influence on the proportion of cryptogenic events among all recurrent CVE.

Results of the present study suggest that a PFO may be causal for the index event, but is unrelated to a considerable proportion of subsequent ischemic events. Other studies indicated that the role of concurrent etiologies for stroke recurrence increases with advancing age at a more rapid pace than does the respective risk of a PFO; however, the risk associated with PFO may also increase because of more thromboses with advancing age.13,14 In our medically treated patients, concurrent etiologies were more frequent in those older than 55 years at the time of the index event than in younger patients.

The frequency of concurrent etiologies for stroke recurrence did not differ between patients with or without coinciding atrial septal aneurysm or those with large or small-to-moderate right-to-left shunt. Previous studies have reported coinciding atrial septal aneurysms15,16 and large PFO size17 to increase risk of stroke recurrence. However, the impact of these markers has not been validated conclusively. For instance, the French Patent Foramen Ovale/Atrial Septal Aneurysm (PFO/ASA) study observed increased rates of stroke recurrence among patients with coinciding atrial septal aneurysm,16 whereas other studies failed to confirm this observation.18,19,20

Following are possible implications of our findings. First, etiologic workup seems to be indispensable after recurrent stroke or TIA, because concurrent stroke etiologies may have emerged or become evident since the index event. Second, given that concurrent stroke etiologies are not prevented by percutaneous device closure of the PFO, we would not discontinue antithrombotic treatment in patients who undergo PFO closure. Accordingly, future randomized controlled trials that compare percutaneous device closure with medical treatment should consider indefinite continuation of antithrombotic treatment in both treatment arms.

Our study has several limitations. First, we present a hospital-based cohort of patients with PFO and otherwise-unexplained stroke that had been treated with antiplatelet drugs, oral anticoagulants, or percutaneous device closure at the discretion of treating physicians or according to patient preference. Therefore, selection and allocation bias are possible. Second, the lack of regularly scheduled follow-up may have led to underestimation of the recurrence rate, especially for TIA. However, the chances of having missed recurrent strokes are small, because overlapping sources of case ascertainment were used whenever possible.

**Conclusions**

Concurrent etiologies are identified for a considerable proportion of recurrent ischemic events. They cast doubt on the sole causal role of PFO in the case of stroke recurrence, and indicate that secondary prevention in patients with crypto-
genic stroke and PFO should not be focused on PFO closure alone.

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References
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