Is Patent Foramen Ovale a Family Trait?  
A Transcranial Doppler Sonographic Study  

Caroline Arquizan, MD; Joël Coste, MD; Pierre-Jean Touboul, MD; Jean-Louis Mas, MD

Background and Purpose—Patent foramen ovale (PFO) is a frequent finding in young patients with stroke. The aim of this study was to assess whether PFO is a family trait.

Methods—Sixty-two consecutive patients younger than 60 years of age with ischemic stroke and 62 age and gender-matched control siblings were examined by means of contrast transcranial Doppler (TCD) of the middle cerebral artery, using a standardized protocol. The reliability of TCD examination in our laboratory was assessed against transesophageal echocardiography (TEE). All TCD recordings were reviewed by a blinded experienced observer from another center. Disagreements between readers were resolved by unblinded consensus review.

Results—Siblings of patients with PFO had a significantly higher prevalence of PFO than had siblings of patients without PFO (61.5% versus 30.6%; OR 3.64 [1.3 to 10.5]; P=0.015). The κ statistics indicated that agreement of pairs (patients/control siblings) was not due to chance. The strength of the association was sex dependent. In women pairs, prevalence of a PFO was 76.5% in siblings of patients with PFO and 25% in siblings of patients without PFO, giving an OR of 9.8 (95% CI 2 to 47.9; P<0.01). In contrast, in men, no significant difference was observed in the prevalence of PFO between siblings of patients with or without PFO (respectively 33.3% and 35%), giving an OR of 0.9 (95% CI 0.2 to 4.9; P=0.9).

Conclusions—This study suggests that, in women, PFO is a family trait. (Stroke. 2001;32:1563-1566.)

Key Words: patent foramen ovale  ■ transcranial doppler  ■ ultrasonics

Patent foramen ovale (PFO) can be detected in approximately 30% of the population. This cardiac abnormality has been shown to be more common in young patients with stroke than in control subjects and seems to be a risk factor for the development of decompression sickness in divers. The origin of this cardiac abnormality is at present unknown, and it is unknown whether PFO is a family trait. If it turns out that PFO is a family trait, this cardiac abnormality could contribute to genetic susceptibility for stroke. In addition, its detection in asymptomatic patients, particularly in relatives of stroke patients, might be useful to counsel them about stroke prevention (for example, to avoid accumulating risk factors for stroke) or activities such as scuba diving.

Transesophageal echocardiography (TEE) with contrast injection is considered the gold standard to detect a right-to-left shunt, presumed to be due to a PFO in the majority of cases. A number of studies have recently shown that contrast-enhanced transcranial Doppler (TCD) examination of the middle cerebral artery is highly sensitive and specific compared with TEE to detect right-to-left shunt. Contrast TCD is a noninvasive and safe technique that does not cause patient discomfort. We used this technique to assess whether the persistence of a PFO is a family trait.

Subjects and Methods

Study Population

Sixty-two consecutive patients admitted to our department for ischemic stroke were enrolled in this study. Inclusion criteria included the following: (1) age between 18 and 60 years; (2) ischemic stroke confirmed by neuroimaging; (3) etiological workup, including TEE with a contrast study; (4) no atrial septal defect of the ostium secundum type at echocardiography; (5) consent to undergo contrast TCD; (6) temporal window suitable for TCD; and (7) presence of a living control sibling of the same sex fulfilling the following criteria: age between 18 and 60 years and within 10 years of patient age; child from the same parents as the index patient; no past history of stroke; no pregnancy; and consent to undergo contrast TCD. When several siblings fulfilled the inclusion criteria, the sibling whose age was nearest to that of the patient was included.

The 62 patients were selected from among 308 patients, aged 18 to 60 years, admitted to our department for ischemic stroke between January 1995 and June 1999. Reasons for exclusion were etiological workup not including TEE with a contrast study, no temporal window suitable for TCD, no atrial septal defect of the ostium secundum type, refusal to undergo TCD examination, no living control sibling of the same sex fulfilling the following criteria: age between 18 and 60 years and within 10 years of patient age; child from the same parents as the index patient; no past history of stroke; no pregnancy; and consent to undergo contrast TCD. The 62 patients selected had a complete etiological workup.

Contrast TCD Protocol

Sixty-two patients with ischemic stroke and 62 control siblings were examined by means of contrast TCD. All TCD examinations were...
performed with an EME TC 2020 (software version 2.1). A 2-MHz pulsed-Doppler transducer was used with a multidepth adapter, which allowed discrimination between true embolic signals and artifacts. Microembolic signals (MES) were defined as characteristic visible and audible (“chirping” or “popping”) short duration high-intensity signals within the Doppler flow spectrum from the middle cerebral artery.12,13 All examinations were recorded on super-VHS videotapes for subsequent playback and analysis.

Every subject was placed in the supine position, and 1 middle cerebral artery was insonated through the temporal window at a depth of 50 to 55 mm. Microcavitation saline contrast was generated by mixing 9 mL of normal saline and 1 mL of air between two 10-mL syringes connected to a 3-way stopcock, which was attached to an intravenous catheter inserted into an antecubital vein. Once the contrast was prepared, it was immediately injected as a bolus with a 2-minute interval between each test, first during normal breathing and then just before a Valsalva maneuver (VM). The patient was asked to start the VM at the end of the injection and to release the strain after 5 seconds. When the result was negative or questionable, the injection was repeated before another VM and, if still negative, during repeated series of 3 to 5 rapid and consecutive coughs, prolonged for 10 seconds. When these tests were negative or doubtful, the whole procedure was repeated in the contralateral middle cerebral artery. The quality of the VM was assessed before the procedure, without contrast injection, by observing the decrease followed by the increase of intracranial blood flow velocity.14

The diagnosis of right-to-left shunt rested on the presence of at least 1 MES within 10 seconds after contrast injection. A semiquantitative TCD score was used to quantify the degree of shunt: no MES, small (<10 MES) within 20 seconds following the detection of first microbubble), intermediate (10 through 50 MES), and massive (>50 MES).

Reliability of TCD Protocol

Comparison of Contrast TCD and Contrast TEE

We assessed the reliability of contrast TCD, compared with contrast TEE in the 62 stroke patients. The TEE protocol examination was performed according to previously described methods.1 We performed all computations using the SAS package (software version 6; SAS Inc.).17 The ethical committee of our institution approved the protocol.

Relevability of TCD Protocol

Comparison of Contrast TCD and Contrast TEE

We assessed the reliability of contrast TCD, compared with contrast TEE in the 62 stroke patients. The TEE protocol examination was performed according to previously described methods.1 The echographic diagnosis of PFO was based on the appearance of more than 5 microcavitations, either spontaneously or after provocative maneuvers, into the left atrium within 3 cardiac cycles of the total opacification of the right atrium. All contrast TCD were performed by a single observer (C.A.), who was blinded to the results of TEE.

Interobserver Variability in Detection of Right-to-Left Shunts With Contrast TCD

All TCD examinations were reviewed independently by an experienced observer from another center (P.-J.T.), who was blinded to the reading of the other observer, the status of the subject (stroke patient or control sibling), and the results of TEE. Disagreements between readers were resolved by unblinded consensus review.

Statistical Analysis

Reliability of TCD Protocol

Sensitivity and specificity of contrast TCD in the detection of a PFO compared with contrast TEE as the gold standard were calculated. Interobserver variability in the detection of a right-to-left shunt and in the semiquantitative TCD scores was assessed by using \( \kappa \) values. Weighted \( \kappa \) values were used for the evaluation of the 4-category variable “degree of shunt.” Quadratic (dis)agreement weights were used for calculating weighted \( \kappa \) statistics. The value of \( \kappa \) can vary from 1 (perfect agreement) to 0 (equivalent to agreement observed by chance) or even −1 (agreement lower than that observed by chance alone).15 Sample size was determined with a formula given by Fleiss16 to ensure narrow CIs for \( \kappa \) values.

Familial Aggregation of PFO

Patients and siblings were compared for age, prevalence of PFO, and degree of shunt, by using \( t \) tests and \( \chi^2 \) statistics as appropriate.

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Results

Reliability of TCD Protocol

With contrast TEE as the gold standard, the sensitivity and specificity of contrast TCD were 90.5% and 82.9%, respectively. Interobserver agreement in the detection of a PFO and in the degree of shunt was very high: observers disagreed on the presence or absence of a PFO in 3 patients (\( \kappa=0.95, 95\% \) CI 0.9 to 1) and on the semiquantitative TCD scoring in 12 patients (\( \kappa=0.89, 95\% \) CI 0.8 to 0.9).

Familial Aggregation of PFO

The demographic characteristics, proportion of PFO, and degree of shunt in stroke patients and control siblings are shown in Table 1. Patients and control siblings were comparable regarding mean age. The prevalence of PFO and the degree of shunt did not differ between groups.

Table 2 shows the proportion of concordant pairs (stroke patient and control sibling) for the presence of a PFO. Siblings of patients with PFO had a significantly higher

| TABLE 1. Characteristics of Stroke Patients and Control Siblings |
|------------------------|-----------------|-----------------|-----------------|
|                       | Patients (n=62) | Siblings (n=62) |
| Sex, M:F              | 29:33           | 29:33           |
| Age (mean±SD), y      | 43.6±11.2       | 42.5±10.9       |
| Patent foramen ovale,*| 26 (42%)        | 27 (44%)        |
| Degree of shunt, n (%)| 36 (58%)        | 35 (56%)        |
| No shunt              | 10 (16%)        | 14 (23%)        |
| Intermediate          | 6 (10%)         | 10 (16%)        |
| Massive               | 10 (16%)        | 3 (5%)          |

* Determined by TCD examination.

The familial aggregation of PFO was analyzed with 2 complementary approaches: (1) in terms of association, ie, addressing the question, “Is the prevalence of PFO increased in siblings of patients presenting with a PFO compared with that in patients without PFO?” and (2) in terms of agreement, which is a different and complementary approach, which takes chance agreement into account. Here the question is, “How concordant are the pairs (patients/siblings) for the presence of PFO?” The first approach involves the calculation of a \( \chi^2 \) test or OR (with 95% CIs).13 ORs indicate the risk of PFO in siblings of patients with PFO compared with that in patients without PFO. In the second approach, we calculated \( \kappa \) statistics.

We performed all computations using the SAS package (software version 6; SAS Inc.).17 The ethical committee of our institution approved the protocol.

TABLE 2. Proportion of Concordant Pairs (Patient/Sibling) for the Presence of a PFO

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Siblings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PFO+</td>
<td>PFO−</td>
</tr>
<tr>
<td>Siblings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFO+</td>
<td>16 (61.5%)</td>
<td>11 (30.6%)</td>
</tr>
<tr>
<td>PFO−</td>
<td>10 (38.5%)</td>
<td>25 (69.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>36</td>
</tr>
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</table>
The detection of a PFO with contrast TCD was very high, with no significant difference being observed in the relative. In addition, young asymptomatic relatives are more likely to benefit from advice or treatment. Siblings with a past history of stroke were excluded because PFO has been associated with ischemic stroke.

To the best of our knowledge, this study is the first to show familial aggregation of PFO. The prevalence of PFO in control siblings was higher (43.5%) than would be expected in the general population (approximately 30%).\textsuperscript{1,3,4} whereas the prevalence of PFO in siblings of probands without a PFO (30.6%) was similar to that in the general population. In addition, the proportion of PFO was 3 times higher in siblings of patients having a PFO than in siblings of patients without PFO, this difference not being by chance. As we selected only 1 sibling for each proband, we could have underestimated the true prevalence of familial PFO (due to variable penetrance).

Whether the selection of young stroke patients may have induce bias in these results is at present unknown. The findings of this study extend the concept that many “apparently nongenetic disorders” have genetic bases and exhibit familial aggregation. PFO, at genetic and pathogenesis levels, may be a form of atrial septal defect, which has a well-established genetic etiology.\textsuperscript{10} The risk of misclassifying atrial septal defects of the ostium secundum type as PFO was very low in our study, because all stroke patients had TEE in addition to contrast TCD to exclude this cause of right-to-left shunt.

Interestingly, familial aggregation of PFO appeared to be higher in women. This finding was unexpected, because the prevalence of PFO is not known to be higher in women in the general population.\textsuperscript{1,3} In view of the small number of pairs in each gender category, the possibility of type-1 error should be raised. The familial aggregation of PFO may also reflect effects of modifying genes or competing environmental risk factors.

In conclusion, this study suggests that PFO is a family trait and may contribute to genetic susceptibility for stroke. However, further studies, including family studies, are needed to confirm our results and to examine the mode of transmission of this septal abnormality. Whether contrast TCD should be recommended in relatives of patients with PFO remains to be established, as there are no data at the present time to support that healthy individuals with PFO need to be treated medically or surgically.

### References


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