Patent Foramen Ovale Size and Embolic Brain Imaging Findings Among Patients With Ischemic Stroke

Michaela M. Steiner, MD; Marco R. Di Tullio, MD; Tanja Rundek, MD; Robert Gan, MD; Xun Chen, MS; Chiara Liguori, MD; Michael Brainin, MD; Shunichi Homma, MD; Ralph L. Sacco, MS, MD

Background and Purpose—Although the cause of stroke among patients with patent foramen ovale (PFO) may be due to paradoxical cerebral embolism (PCE), this mechanism is often difficult to prove. The aim of our study was to evaluate the association between brain imaging findings suggestive of embolism and PFO among ischemic stroke patients.

Methods—As part of the Northern Manhattan Stroke Study, 95 patients with first ischemic stroke over age 39 underwent transesophageal echocardiography (TEE) for evaluation of a cardiac source of embolism. The stroke subtype was determined by modified NINDS Stroke Data Bank criteria. Stroke subtype and MRI/CT imaging data were evaluated blind to the presence of a PFO. These findings were compared between two groups: patients with medium to large PFO (≥2 mm) and small (<2 mm) or no PFO.

Results—Of the 95 patients who underwent TEE, 31 (33%) had a PFO. The frequency of PFO was significantly greater among patients with cryptogenic infarcts (19 of 42; 45%) compared with patients with determined cause of stroke (12 of 53, 23%; P = 0.02). Medium to large PFOs were found more often among cryptogenic strokes than among infarcts of determined cause (26% versus 6%; P = 0.04). Superficial infarcts occurred more often in the group with larger PFOs than in the group with small or no PFOs (50% versus 21%; P = 0.02). Patients with medium or large PFOs more frequently had occipital and infratentorial strokes (57% versus 27%; P = 0.02).

Conclusions—Stroke patients with larger PFOs show more brain imaging features of embolic infarcts than those with small PFOs. Larger PFOs may be more likely to cause paradoxical embolization and may help explain the stroke mechanism among patients with no other definite cause. (Stroke. 1998;29:944-948.)

Key Words: cerebral infarction ▪ echocardiography, transesophageal ▪ foramen ovale, patent

Patent foramen ovale (PFO) has long been recognized as a potential risk factor for ischemic stroke through paradoxical cerebral embolism (PCE). Case-control studies demonstrating a higher prevalence of PFO among patients with cryptogenic strokes led to the acceptance of PFO as stroke risk factor. However, when transesophageal echocardiography (TEE) (the most sensitive technique for detecting a PFO) is used, the prevalence of PFO in the normal population is high (between 22 and 38%). Therefore, the detection of a PFO in a stroke patient does not necessarily identify the cause for the stroke.

Establishing a causal relationship between PFO and stroke remains the crucial point in the diagnosis of PCE. The suggested criteria for this diagnosis (systemic or cerebral embolism in the absence of a left-sided cardiac origin; presence of a venous thrombosis; documentation of a right-to-left cardiac shunt; occurrence of an elevated right heart pressure) may not always be met. The presence of other cofactors, such as the size of a PFO, may raise the probability of PCE.

Brain imaging findings could also contribute to the evaluation of the role of the PFO as the mechanism for stroke. If PCE is the pathogenic mechanism of the event, brain imaging should more often be compatible with embolism in patients with rather than those without a PFO. Only anecdotal data are available on brain imaging findings among patients with ischemic stroke and PFO; no study specifically investigating these findings has been conducted.

In our study, we evaluated the brain imaging findings and the vascular distribution of ischemic strokes among patients in whom a PFO was diagnosed by TEE in order to determine whether the cerebral infarction was likely to be embolic and, therefore, supportive of a diagnosis of PCE.
Subjects and Methods

Study Population

The patients in this study were selected from the Northern Manhattan Stroke Study, which has been described previously. Patients eligible for this analysis were those who were prospectively enrolled from February 1993 to December 1996 if they met the following criteria: (1) diagnosed with acute cerebral infarction, (2) over the age of 39 years at stroke, (3) resident of the Northern Manhattan community, and (4) had undergone TEE.

Reasons for referral for TEE included presentation with embolic syndrome without an obvious source of embolism, unexplained stroke, or conflicting data regarding the potential stroke mechanism. Moreover, younger patients with unexplained stroke were more likely to be referred for TEE than older stroke patients. Patients who were obtunded, unable to swallow, or uncooperative were ineligible for the procedure. (Approximately 15% to 20% of all acute stroke patients admitted to the Neuromuscular Unit are usually referred for TEE.)

Index Stroke Evaluation

Patients were examined within a week of stroke onset by one of the study neurologists. Data were collected through an in-person interview of the patient or family and review of the hospital records. Details of medical, neurological, and social history; stroke risk factors; general and neurological examinations; and laboratory studies were ascertained. Diagnostic evaluations included head CT at admission; ECG; extracranial duplex Doppler ultrasonography; transcranial Doppler; two-dimensional transthoracic ECG; and when necessary, a follow-up CT or MRI, Holter monitor, conventional cerebral angiogram, or MR angiogram.

A systematic assessment of lower extremity venous Doppler was not performed; however, none of our study patients had clinical signs of lower extremity venous thrombosis.

Stroke Subtype Classification

The stroke subtype was determined by a diagnostic committee after review of all the available data to characterize each ischemic stroke by causal mechanism based on a modified NINDS Stroke Data Bank scheme. The project coordinator prepared the data, which included admitting clinical syndrome and results of blood tests, brain imaging, and noninvasive cardiac and vascular evaluation. The committee members were blinded to the identifying patient data, gender, race/ethnicity, risk factors (except for history of transient ischemic attack, atrial fibrillation, and recent myocardial infarction) including presence of patient foramen ovale, and outcome. Ischemic strokes were classified into the following categories, which have been characterized previously: infarction due to extracranial or intracranial atherosclerosis, embolism from a commonly accepted cardiac source, lacunar infarction, cryptogenic infarction, conflicting mechanisms, and stroke from other unusual causes. Patients classified as having cryptogenic infarction had no definite cardioembolic source or obvious ipsilateral atherosclerotic vascular disease, and they usually presented with a nonlacunar syndrome and an infarct of unexplained cause. They failed to meet any of the criteria for infarcts of determined cause or may have had inadequate evaluation so that reasonable diagnostic classification was difficult.

Brain Imaging

The first positive brain imaging or a negative scan after an appropriate time from the onset of symptoms was reviewed. The brain imaging features analyzed in this study were the following: number of lesions seen; number of lesions clinically related to the stroke; side, type, size, and site of the relevant lesion; and hemorrhagic transformation of the infarct. Side of the lesion was categorized as left, right, midline, or both. The type of lesion was defined as superficial (if the cortex was mainly involved), superficial and deep (with additional involvement of white matter), deep small (if ≤1 cm), or deep large (if >1 cm). The size of the lesion was classified as ≤1 cm, ≤1/2 lobe, ≤1 lobe, or >1 lobe. Possible sites included the frontal lobe, parietal lobe, temporal lobe, occipital lobe, basal ganglia, thalamus, corona radiata/centrum semiovale, internal capsule, midbrain, pons, medulla, and cerebellum. Hemorrhagic transformation was determined by the hyperdensity in the infarct area on CT or on MRI suggestive of a hemorrhagic stroke. On the basis of these results, the diagnostic committee classified the vascular territory of the infarct: internal carotid artery (ICA), anterior cerebral artery (ACA), posterior cerebral artery (PCA), PCA penetrant, middle cerebral artery (MCA), MCA penetrant, MCA stem, MCA upper division branch, MCA lower division branch, basilar, basilar penetrant, vertebral/posterior inferior cerebellar (PICA), or other. An infarct in the territory of the ICA, ACA, PCA, MCA, basilar, or vertebral/PICA was classified as infarct of a major vessel. For the purpose of the analysis vascular territory were categorized into 2 categories, anterior and posterior.

Echocardiography and Diagnosis of PFO

Echocardiography was performed with a Hewlett-Packard Sonos 1000 or 2500 equipment with a 5.0-MHz biplane or omniplane transducer for transesophageal imaging. We performed both color Doppler and contrast study for the detection of PFO. The diagnosis of PFO was based on findings from the contrast study, which has been reported to be more sensitive than color Doppler. Contrast material was prepared by mixing 10 mL saline with 0.5 mL air by means of two syringes mounted on a 3-way stopcock. During the test, the suspension was rapidly injected into an antecubital vein. A PFO was considered to be present when at least 1 microbubble was seen in the left atrium within 3 cardiac cycles from their appearance in the right atrium. The test was repeated during Valsalva maneuver to increase its sensitivity whenever patients were able to perform it. Otherwise, the test was repeated during coughing. For transesophageal imaging, the longitudinal plane was selected to display the fossa ovalia area; the maximum separation of septum primum and secundum was measured in this view. PFO size was classified into 3 categories according to the criteria used at the Echocardiography Laboratory of the Columbia–Presbyterian Medical Center: small (when the separation was 0 to 1.9 mm), medium (from 2 to 3.9 mm), and large (≥4 mm).

Statistical Analyses

Frequencies of stroke subtypes, brain imaging, and vascular findings were calculated for the patients with PFO and those without PFO. According to PFO size, the patients were classified into a group with medium and large PFOs and a group with small or no PFOs. To compare the proportions of brain imaging and vascular findings between those 2 groups, the χ² test was used. The Fisher exact test was used when the expected cell count was <5. Statistically significant difference was set at the level of P<0.05.

Results

Of 584 patients with first ischemic stroke, 95 (mean age, 64.4±11.1; 52% women) underwent TEE for evaluation of a cardiac source of embolism. A comparison between patients in whom TEE was and those in whom TEE was not performed disclosed no significant difference by stroke subtype and gender. Patients with TEE evaluation were younger (mean age, 64) than those without TEE (mean age, 70 years).

A PFO was detected among 31 patients (33%; mean age, 64.2±10.0) whereas 64 patients (67%) had no PFO (mean age, 64.6±11.7). All patients had undergone at least 1 brain imaging, and the mean time of investigation after onset of stroke symptoms was 2.5±3.6 days for CT and 3.4±2.5 days for MRI. The diagnosis of the infarct was based on CT in 54 cases (57%) and MRI in 41 (43%). The frequencies of PFO among the stroke subtypes are shown in Table 1. The frequency of PFO was significantly higher in patients with...
cryptogenic infarcts (19 of 42; 45%) compared with patients with determined cause of stroke (12 of 53, 23%; \( P = 0.02 \)).

Overall, the type, site, size, and number of responsible lesions, as well as the frequency of hemorrhagic transformation and the vascular territory of the infarct, were similar between patients with PFO and without PFO. When we analyzed cryptogenic infarcts only, we also did not find any statistically significant difference in the criteria described above.

Of the 31 patients with PFO, 17 (55%) had a small (0 to 1.9 mm) PFO, 11 (35%) had a medium (2 to 3.9 mm) PFO, and 3 (10%) had a large (\( \geq 4 \) mm) PFO. The prevalence of PFOs of medium and large size was greater among cryptogenic infarcts (11 of 42; 26%) than in infarcts of determined cause (3 of 54, 6%; \( P = 0.04 \)).

Since small PFOs may not have the same stroke risk as large PFOs, we reclassified the PFO status among the 95 stroke patients into 2 groups: 1 group consisted of patients with medium and large PFOs (\( n = 14 \)), and the other group (\( n = 81 \)) had either no PFOs or small PFOs. Table 2 shows the imaging and vascular findings in these two groups of patients. Superficial infarcts occurred more often in the group with larger PFOs (7 of 14; 50%) than in the small or no PFO group (18 of 81, 21%; \( P = 0.02 \)). There was a tendency toward larger infarcts (>1 lobe) in patients with larger PFOs (2 of 14; 14%) compared with patients with no or small PFOs (2 of 81, 2%; \( P = 0.10 \)). In medium and large PFO group, the site of stroke was significantly more occipital and infratentorial (8 of 14; 57%) than in the group with no or small PFOs (20 of 81, 27%; \( P = 0.02 \)). Larger vessels were more often affected in the group with larger PFOs (9 of 14; 64%) and less often in the group with smaller PFOs (27 of 81, 33%; \( P = 0.05 \)). The posterior circulation was more often involved in the group with larger PFOs (9 of 14; 64%) and less often in the group with no or small PFOs (27 of 81, 33%; \( P = 0.05 \)). No difference was seen between the 2 groups with regard to the side of lesion and the frequency of hemorrhagic transformation.

The separate analysis of cryptogenic infarcts showed trends similar to those of the overall group, but no statistically significant difference was achieved.

**Discussion**

A paradoxical embolism is expected to cause brain infarcts that are similar on brain imaging to those caused by other embolic sources. Some features on brain imaging are more likely to indicate an embolic infarct. If a superficial arterial branch is occluded or if there is an infarct >1 lobe in size, the presence of an embolic infarct is strongly suggested. When we compared the brain imaging findings between patients with PFO and those without, we found no differences concerning findings of embolic infarcts. This implies that the mere presence of a PFO may not be an indication of the cause

<table>
<thead>
<tr>
<th>Stroke Subtype</th>
<th>Infarcts of determined cause</th>
<th>Cryptogenic infarcts</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n%</td>
<td>n</td>
</tr>
<tr>
<td>Atherosclerotic</td>
<td>22</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td>Lacunar</td>
<td>16</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>13</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Conflicting mechanism</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cryptogenic infarcts</td>
<td>42</td>
<td>19</td>
<td>45</td>
</tr>
<tr>
<td>Total</td>
<td>95</td>
<td>31</td>
<td>33</td>
</tr>
</tbody>
</table>

**TABLE 1. Frequencies of PFO Among Stroke Subtypes**

<table>
<thead>
<tr>
<th>Stroke Subtype</th>
<th>Strokes, n</th>
<th>PFO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarcts of determined cause</td>
<td>n</td>
<td>n%</td>
</tr>
<tr>
<td>Atherosclerotic</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
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<td>Conflicting mechanism</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cryptogenic infarcts</td>
<td>42</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>95</td>
<td>31</td>
</tr>
</tbody>
</table>

PFO indicates patent foramen ovale.

**Table 2. Brain Imaging Findings Among Patients With TEE (n=95)**

<table>
<thead>
<tr>
<th>Brain Imaging</th>
<th>Medium or Large PFO (n=14)</th>
<th>No or Small PFO (n=81)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial infarct</td>
<td>7 (50)</td>
<td>18 (21)</td>
<td>0.02</td>
</tr>
<tr>
<td>Size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1 lobe</td>
<td>2 (14)</td>
<td>2 (2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occipital/brainstem/cerebellar</td>
<td>8 (57)</td>
<td>20 (27)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hemispheric, not occipital</td>
<td>4 (29)</td>
<td>25 (31)</td>
<td></td>
</tr>
<tr>
<td>Basal ganglia, internal capsule, or thalamus</td>
<td>2 (14)</td>
<td>30 (37)</td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>0 (0)</td>
<td>6 (7)</td>
<td></td>
</tr>
<tr>
<td>Number of infarcts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 clinically relevant lesion</td>
<td>11 (85)</td>
<td>64 (85)</td>
<td>1.0</td>
</tr>
<tr>
<td>Vascular findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large artery territory*</td>
<td>9 (64)</td>
<td>31 (38)</td>
<td>0.05</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>9 (64)</td>
<td>27 (33)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

PFO indicates patent foramen ovale.

*Infarcts in the territory of the internal carotid artery, anterior cerebral artery, middle cerebral artery, posterior cerebral artery, basilar artery, or vertebral/posterior inferior cerebellar.
of the stroke in these patients. Embolic brain imaging features, however, were more frequently found among patients with large PFOs. Since the size of a PFO may be an important modifying factor of the stroke risk, we categorized the patients into 2 groups: those with medium or large PFOs and those with small or no PFOs.

We found PFOs of medium and large size more frequently in cryptogenic infarcts, whereas the distribution of small PFOs seemed to be equal between cryptogenic infarcts and infarcts of defined cause. Homma et al investigated 24 patients with PFO by TEE and also found significantly larger PFOs (2.1 ± 1.7 mm) in patients with cryptogenic infarcts than in patients with an identifiable cause of stroke (0.57 ± 0.78 mm). Another study demonstrated a different morphologic appearance of PFOs in cryptogenic strokes from PFOs in a control group. From these results as well as the results of the present study, an association between the size of PFO and the probability of PCE could be hypothesized, in the sense that larger PFOs are probably more likely than small PFOs to cause paradoxical cerebral embolism.

We found features of embolic infarcts, such as more superficial infarcts, larger infarcts, and infarcts in territories of large vessels, more often in patients with large PFOs than in patients with small or no PFOs. No differences were seen in the number of clinically relevant lesions and hemorrhagic transformation of the infarct. Despite the fact that the presence of hemorrhagic transformation is a strong indicator for embolic infarction, a previous published study also did not demonstrate an association between PFO and hemorrhagic infarcts. The reason we did not find any differences regarding hemorrhagic transformation between patients with and without PFO might result from the small sample size and relatively low frequency of hemorrhagic infarctions. Moreover, only the first pathological imaging was taken into consideration, and the time span from onset of symptoms to brain imaging might have been too short to detect a higher percentage of hemorrhagic transformation.

Several studies have suggested that embolic infarcts may affect the posterior cerebral artery in approximately 35% of cases and the cerebellum in up to 54%. In one transcranial Doppler study of 12 patients with PFO, microcavitations from contrast injection were detected in the MCA of all patients and in the posterior circulation in 75% of the patients. In our study, the posterior circulation was more frequently involved in patients with larger PFOs, suggesting the possibility that paradoxical embolization may account for some of these findings.

Among the cryptogenic infarct subgroup, the results regarding the association between PFO and stroke size and distribution were similar to those of the overall group, but the smaller sample size limited the ability to reach statistical significance. We found a greater frequency of PFOs in patients with cryptogenic strokes than in patients with known cause of stroke. This confirms that the role of a PFO as a risk factor for stroke may be greater in patients in whom no other cause is found.

As there were more features of embolic infarcts found in larger PFOs, we suggest that a PFO of medium or large size could be a pathway for PCE. Small PFOs are probably less likely to cause paradoxical embolism. This could be due to the fact that small PFOs in most cases might not be hemodynamically functional and therefore not allow the passage of even small emboli.

The findings of our study suggest that some cryptogenic strokes might be reclassified as cardioembolic on the basis of the detection of a PFO and brain imaging findings suggestive of embolism. However, such reclassification should not be performed routinely but should instead be made on an individual case basis, taking into consideration other associated factors, such as deep venous thrombosis or blood hypercoagulability, that might affect the diagnosis.

Our study has several limitations. First, the association between imaging findings and embolic origin of an infarct must be considered with some caution, since a wider variety of sizes and types of lesions can be associated with an embolic infarct. Also, our sample size was relatively small, especially for cryptogenic infarcts. Furthermore, since the mean age of patients in our study was 64 years and only those over 39 were included in the study, our findings cannot be generalized to a younger population of patients with stroke.

In summary, we conclude that the presence or absence of a PFO alone may not be a sufficient finding in itself to suggest paradoxical cerebral embolism as the cause for the stroke. The measurement of the size of the PFO and the presence of embolic brain imaging findings could provide further information on the significance of PFO as a potential cause of stroke. A possible causal relationship between PFO and stroke should be suspected in the presence of a large PFO and no other definite cause of stroke.

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References
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