Patent Foramen Ovale and Brain Infarct
Echocardiographic Predictors, Recurrence, and Prevention

Joseph P. Hanna, MD; Jing Ping Sun, MD; Anthony J. Furlan, MD; William J. Stewart, MD; Cathy A. Sila, MD; Ming Tan, PhD

Background and Purpose
Paradoxical embolism through a patent foramen ovale is a recognized cause of stroke, but clinical predictors, recurrence rate, and prevention of brain infarcts in patients with patent foramen ovale have not been determined. We reviewed transesophageal echocardiographic records to ascertain echocardiographic predictors and optimal prophylaxis for patent foramen ovale-related infarcts.

Methods
A patent foramen ovale was identified in 74 patients during 615 transesophageal echocardiograms by color Doppler or saline contrast during a 60-month period. On the basis of final clinical situation, the patients were divided into the following groups: group 1, infarct with patent foramen ovale a likely cause (n=16); group 2, infarct with patent foramen ovale an unlikely cause (n=23); and group 3, no infarct (n=35). Transesophageal echocardiograms were reviewed to assess patent foramen ovale characteristics and associated cardioembolic sources without knowledge of clinical details or group assignment. Follow-up after a patent foramen ovale-related infarct was obtained by telephone or written correspondence in 15 of 16 group 1 patients.

Results
Atrial septal aneurysms were more common in group 1 (38%) compared with group 2 (10%) and group 3 (8%) (P=.02). Contrast right-to-left shunting occurred in 88% of group 1 (P=.06) and 86% of group 2 (P=.07) compared with 60% of group 3. Prevention of recurrence in subjects with presumed patent foramen ovale-related brain infarcts varied. Aspirin was usually chosen after initial brain ischemia. Warfarin and patent foramen ovale closure were usually reserved for subjects with symptoms of brain ischemia while taking aspirin or those who required warfarin or cardiac surgery for other indications. No recurrent infarcts occurred in 15 patients during a mean follow-up period of 28 months.

Conclusions
Atrial septal aneurysm and right-to-left shunt may be predictive of a patent foramen ovale that predisposes a patient to stroke. Aspirin may provide sufficient infarct prophylaxis after initial ischemia. Warfarin and surgical correction should likely be reserved for those in whom aspirin is not effective or those who require warfarin or cardiac surgery for other reasons until prospective studies are available.

Key Words • cerebral infarction • echocardiography • foramen ovale, patent

The aim of this study was to detect echocardiographic features that predispose a patient to a presumed PFO-related infarct. Our experience in treating patients after a PFO-related infarct is also discussed.

Subjects and Methods
We reviewed TEE records from June 1987 to July 1992, identifying patients with PFO diagnosed by either color Doppler or saline contrast echocardiography. PFOs were detected in 77 of 615 consecutive studies. Three subjects had a PFO identified twice. TEE was obtained in 34 patients to assess for a cardioembolic source. The remaining 40 patients underwent TEE for the following reasons: mitral valve evaluation (17), atrial septal defect evaluation (7), pulmonary hypertension etiology (2), aortic valve evaluation (2), restrictive cardiomyopathy etiology (2), valvular vegetations (2), and other primary cardiac indications (8). Five of these 40 patients had a remote stroke of presumed etiology other than patent foramen ovale.

Transesophageal echocardiography was performed with a 5-MHz phased probe incorporated into a 110-cm flexible gastroscope interfaced to either a Hewlett-Packard 77030A or an Acuson echocardiograph. The probe was passed 25 to 35 cm from the incisors to obtain an image of both atria with the interatrial septum perpendicular to the tomographic plane. The PFO was identified by transseptum contrast passage, color flow through the atrial septum (Figure), or both.

Saline contrast echocardiography was performed by rapid bolus injection of 10 mL agitated normal saline through an antecubital vein. An adequate study required dense right atrial opacification with contrast medium. Right-to-left shunting was present when contrast was seen in the left atrium at the fossa.
Two-dimensional transesophageal echocardiographic (TEE) images of a patient with a patent foramen ovale, from a longitudinal plane, showing the defect (arrowheads). LA indicates left atrium; RA, right atrium.

owals within three cardiac cycles of right atrial opacification. Routine TEE with pulsed-wave and color-flow Doppler was then performed. The PFO two-dimensional diameter was measured by digitizing stop-frame images. Each study was assessed blindly, without knowledge of group assignment or clinical scenario.

Patients were assigned to three groups by record review and written or telephone correspondence. Historic verification and follow-up were achieved in 70 (95%) of 74 patients. Stroke preventive therapy, compliance, and outcome were obtained in 15 (94%) of 16 patients with an infarct likely related to their PFO (group 1).

Patients with a brain infarct greater than 1 cm maximal diameter as demonstrated by neuroimaging, without evidence of appropriate significant atherosclerosis, atrial fibrillation, intracardiac thrombus, hypercoagulable disorder, vasculopathy, or other well-recognized causes of brain infarct, were included in group 1. One subject in group 1 also had a renal artery occlusion without an alternative cause. Patients who had an alternative, well-recognized cause of brain infarct other than PFO were assigned to group 2. Group 3 consisted of individuals with PFOs by TEE but without history of infarct.

Patients with presumed PFO-related infarcts underwent either lower-extremity ultrasound (62%) or venogram (25%) to detect deep vein thrombosis (DVT). Two patients with presumed PFO-related infarcts did not have lower-extremity venous imaging. Subjects without suspected paradoxical embolism underwent lower-extremity venous imaging only when a DVT was clinically suspected. Pulmonary hypertension was diagnosed when cor pulmonale was present on electrocardiography.

The proportions of TEE-detectable right-to-left shunting (spontaneous and induced by Valsalva maneuver), PFO two-dimensional diameter, atrial septal aneurysm, MVP, and left atrial enlargement were calculated for each group. The proportions of atrial septal aneurysms and right-to-left shunting were compared using Fisher's exact test between group 3 and either group 1 or group 2. Two subjects in group 2 were excluded from echocardiographic comparison because a PFO was not detected during TEE review.

Results

Symptomatic infarcts occurred in 39 (53%) of the 74 patients. Infarcts occurred in 54% of women and 52% of men. The majority of infarcts (59%) were likely due to causes other than those related to PFO. Multiple vascular territories were involved in 6% (1/16) of group 1 and 22% (5/23) of group 2 patients. The presumed etiologies for brain infarct in group 2 included other cardioembolic sources (13), ath erosclerosis (4), carotid dissection (3), and other vasculopathies (3). Patients in group 1 were 23 years younger than those in group 2 and 13 years younger than those without infarcts (Table 1). Lower-extremity DVTs were detected in 5 (31%) of 16 group 1 patients compared with 1 (4%) of 23 group 2 patients and 1 (3%) of 35 group 3 patients. Two patients had cor pulmonale and pulmonary hypertension: one without a stroke and the other with an infarct presumed to be of atheroembolic origin.

Seventeen brain or presumed embolic systemic infarcts were imaged among the 16 group 1 patients: 9 carotid circulation, 7 vertebrobasilar circulation, and 1 renal artery. One patient had infarcts in both the carotid and vertebrobasilar circulations.

Transesophageal echocardiographic characteristics were compared between group 3 and either group 1 or group 2 using Fisher's exact test between each pair. Contrast right-to-left shunting was detected in 88% of group 1 (P=.06) and 86% of group 2 (P=.07) compared with only 60% of group 3 patients (Table 2). Spontaneous paradoxical interatrial shunting occurred in 64%, 78%, and 76% of groups 1, 2, and 3, respectively. The remainder of paradoxical shunts were detected only during the Valsalva maneuver. Doppler right-to-left shunting was absent in group 1 but occurred in 10% of group 2 and 17% of group 3.

Atrial septal aneurysms were present in 38% of group 1 (P=.02) and 10% of group 2 (P=1.00) compared with 8% of group 3. Only 1 subject in group 1 (6%) had neither a right-to-left shunt nor an atrial septal aneurysm; these two findings were absent in 10% of group 2 and 37% of group 3. PFO two-dimensional diameter and the prevalence of MVP and left atrial enlargement were greatest in group 3 (Table 2).

Patients with infarcts likely secondary to PFO were followed up for an average of 28±13 months. Stroke prophylactic therapy varied among these patients and included aspirin, warfarin, open surgical closure, or closure with a septal occlusion device after identification of PFO (Table 3).

Aspirin (325 mg/d) was chosen for stroke prophylaxis in 6 patients. In all 6 the identifying infarct was their initial event. One subject had an inferior vena cava filter placed for a detected DVT before the clipping of an asymptomatic berry aneurysm. No recurrent ischemic symptoms or complications of therapy occurred during 23±9 months of follow-up.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Median Age, y</th>
<th>Range</th>
<th>F</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: PFO likely cause of infarct</td>
<td>16</td>
<td>43</td>
<td>24-75</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>2: PFO unlikely cause of infarct</td>
<td>23</td>
<td>66</td>
<td>38-89</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>3: No infarct</td>
<td>35</td>
<td>56</td>
<td>26-80</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>74</td>
<td>56</td>
<td>24-80</td>
<td>28</td>
<td>46</td>
</tr>
</tbody>
</table>

PFO indicates patent foramen ovale.
TABLE 2. Patent Foramen Ovale and Brain Infarct Demonstrated by Transesophageal Echocardiography

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>R→L Shunt Bubble No.</th>
<th>%</th>
<th>R→L Shunt Doppler No.</th>
<th>%</th>
<th>PFO 2-D Diameter, mm (mean±SD)</th>
<th>ASA No.</th>
<th>%</th>
<th>MVP No.</th>
<th>%</th>
<th>LAE No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>14</td>
<td>88</td>
<td>0</td>
<td>0</td>
<td>1.3±0.5</td>
<td>6</td>
<td>38</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.06*</td>
<td></td>
<td></td>
<td>0.02*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>18</td>
<td>86</td>
<td>2</td>
<td>10</td>
<td>1.2±0.4</td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>24</td>
<td>7</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>0.07*</td>
<td></td>
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<td>1.00*</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>21</td>
<td>60</td>
<td>6</td>
<td>17</td>
<td>1.9±1.0</td>
<td>3</td>
<td>8</td>
<td>11</td>
<td>31</td>
<td>20</td>
<td>57</td>
</tr>
</tbody>
</table>

R→L indicates right-to-left; PFO, patent foramen ovale; 2-D, two-dimensional; ASA, atrial septal aneurysm; MVP, mitral valve prolapse; LAE, left atrial enlargement; group 1, PFO likely cause of infarct; group 2, PFO unlikely cause of infarct; and group 3, no infarct.

Compared with group 3 using Fisher’s exact test.

Warfarin targeted for a prothrombin time of 1.3 to 1.5 times control (international normalized ratio, 2.0 to 3.0) was begun in 7 patients after identification of PFO. One patient who had a DVT and a pulmonary embolus 1 month before the stroke had stopped warfarin because of melena. Two patients had a DVT detected during the peri-infarct period. One of the 2 was taking an adult aspirin daily before the infarct. The other discontinued warfarin after 6 months because of peptic ulcer hemorrhaging and did not initiate other treatment. Two other patients were receiving one adult aspirin per day before their identifying infarct. Two patients had only one ischemic event. The warfarin of 1 of these 2 patients was replaced with aspirin after 6 months; the other continued to take warfarin. No ischemic symptoms have recurred in these 7 patients during 32±21 months of follow-up.

The PFOs of 2 patients were closed. One patient had surgical closure done at the time of pulmonary valve repair for pulmonic stenosis. The other patient, who was allergic to aspirin and unwilling to continue warfarin, had a septal occlusion device placed transumlinantly after recurrent ischemia while noncompliant on warfarin (prothrombin time, 11.9). Neither patient had a recurrent infarct or therapeutic complication during 49 and 30 months of follow-up, respectively.

Discussion

We discovered a fourfold increase in atrial septal aneurysms in patients with infarcts caused by PFO. Atrial septal aneurysms are found in approximately 1% of autopsy cases and 8% of TEEs performed for a presumed stroke. Atrial septal aneurysms have been associated with right-to-left shunting via a PFO and an increased risk of presumed embolic brain infarcts. Erythrocyte-laden and platelet-fibrin thrombi occur within the aneurysms. Atrial septal aneurysms may predispose to thromboembolism via intra-aneurysmal thrombus or paradoxical venous embolism via an associated PFO. Whether atrial septal aneurysms associated with PFO and right-to-left shunting are larger and more prone to intra-aneurysmal thrombus formation is unknown.

Right-to-left shunting was more common in patients with infarcts that were likely caused by PFO. Right-to-left shunting predisposes a patient to infarction by paradoxical embolization of venous thrombi or other material. Echocardiographic identification of right-to-left shunting is often required to diagnose paradoxical embolism. TEE, although the most sensitive technique for shunt detection, did not detect a right-to-left shunt in 12% of patients with an infarct believed to be secondary to PFO. The absence of detectable right-to-

TABLE 3. Preventive Therapy in Patients With Patent Foramen Ovale as a Likely Cause of Stroke

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>Reasoning</th>
<th>Duration of Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>6</td>
<td>First event</td>
<td>23±9*</td>
</tr>
<tr>
<td>Warfarin</td>
<td>5</td>
<td>325 mg aspirin ineffective (3); first event (1); concurrent DVT (1)</td>
<td>32±21*</td>
</tr>
<tr>
<td>Warfarin, then other</td>
<td>2</td>
<td>Stopped warfarin after 6 months (PUD), no treatment since (1)</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Switched to aspirin after 8 months (first event) (1)</td>
<td>11</td>
</tr>
<tr>
<td>Closure</td>
<td>2</td>
<td>PUD and pulmonic valve stenosis requiring valvuloplasty (1)</td>
<td>49</td>
</tr>
<tr>
<td>Open heart</td>
<td></td>
<td>Aspirin allergy, noncompliant on warfarin (1)</td>
<td>30</td>
</tr>
<tr>
<td>Septal occlusion device</td>
<td>15</td>
<td></td>
<td>28±13</td>
</tr>
</tbody>
</table>

DVT indicates deep vein thrombosis; PUD, peptic ulcer disease. Numbers in parentheses indicate number of patients.

*Mean±SD.
left shunting can be explained by insufficient effort on the Valsalva maneuver, insensitivity of TEE to small amounts of shunting, or an infarct mechanism other than paradoxical embolism.

Patent foramen ovale size was smaller in group 1 patients. In addition, both Doppler-detected and spontaneous contrast–detected paradoxical interatrial shunts were more common in both those without infarct and those with stroke of other presumed etiology. These findings reflect the importance of any right-to-left interatrial shunting and not PFO size in the pathogenesis of paradoxical thromboembolism. Whether increasing PFO size in subjects with a right-to-left shunt increases paradoxical flow, thereby augmenting the risk for paradoxical embolism, requires further investigation.

Mitrail valve prolapse occurred in nearly one quarter of patients with a PFO, compared with a prevalence of 2.5% to 7% in the general population. Others have also detected an increased prevalence of MVP in subjects with PFO compared with the general population. In our cohort MVP occurred most commonly in those without infarcts and was absent in all but one patient with a presumed PFO-related infarct, reaffirming that PFO-related infarcts are not necessarily secondary to MVP.

The younger median age of patients suspected of having a PFO-related infarct can be explained in several ways. Older patients with PFO-related infarcts may have been incorrectly assigned to group 2 because of an increased incidence of both atherosclerosis and cardiac disease with increasing age. Conversely, younger individuals may have been incorrectly assumed to have PFO-related infarcts because of the relatively high frequency of PFO and a failure to detect alternative stroke mechanisms. PFO-related infarcts theoretically should increase with age considering the increased duration of cardiac anomalies and the increased incidence of DVT, pulmonary hypertension, and atrial septal aneurysms in older subjects.

Deep venous thrombosis was undetected in a majority of patients with PFO-related infarcts. Others have also been unable to detect DVT in a majority of patients with presumed paradoxical pulmonary emboli. A low DVT detection rate may reflect transient formation of DVT and subsequent embolization, ultrasonographic insensitivity for lower-extremity DVT, thrombus formation outside the lower extremities, or true absence of a venous source.

Pulmonary hypertension, which is often considered integral to the diagnosis of paradoxical embolism, was not diagnosed in any of the patients with PFO-related infarcts. However, pulmonary hypertension is often undiagnosed because of the insensitivity of the electrocardiogram to early pulmonary hypertension and mild right ventricular hypertrophy. Pulmonary circulation pressures probably increase gradually in the evolution of pulmonary hypertension and eventual cor pulmonale. Paradoxical shunting reflecting increased pulmonary arterial pressure was more common in subjects with than in those without pulmonary embolism. This indicates that TEE-detected paradoxical shunting is probably a more sensitive indicator for pulmonary arterial hypertension and elevated right heart pressures. Also, the absence of cor pulmonale on the electrocardiogram does not preclude the presence of pulmonary hypertension sufficient to cause paradoxical shunting.

Why a PFO remains silent for many years and then becomes pathogenic is unknown. However, both PFO size and atrial septal aneurysm prevalence increase with increasing age as does pulmonary hypertension. Exceeding a critical threshold in the evolution of these anomalies along with the increased tendency for deep venous clot formation with age may predispose subjects to thromboembolic infarcts. Finally, the cumulative risk of paradoxical embolism increases with the number of years of exposure to the right-to-left interatrial shunt.

The recurrence rate after a PFO-related infarct appears to be low, and the influence of various therapies is unknown. No patient had a recurrent infarct detected during a mean period of more than 2 years regardless of the prophylactic therapy prescribed. Others have also recorded a low recurrence rate with medical therapy. No symptomatic infarcts occurred in 36 patients during a mean follow-up of 8.4 months after attempted transcatheter closure. The absence of recurrent infarcts likely reflects the low risk of recurrence regardless of therapeutic intervention.

This study is limited by both the small sample size and the retrospective nature of the study. Therefore, conclusions regarding optimal prophylactic therapy for paradoxical embolism cannot be made. Our echocardiographic comparison may be limited by group assignment bias and a symptomatic control group. Combining groups 1 and 2 (all patients with infarcts) eliminates bias based on presumed infarct pathogenesis. A comparison between all patients with and those without infarcts still reveals an increased incidence of both right-to-left shunting and atrial septal aneurysms in patients with infarcts. Group 3 was not an age-matched, asymptomatic control and had a high incidence of mitral valve and left heart dysfunction. However, both atrial septal aneurysms and pulmonary hypertension predisposing to paradoxical shunting increase with age. Therefore, the significance of both atrial septal aneurysms and right-to-left shunting in patients with infarcts is likely underestimated. The control group's preponderance of mitral valve dysfunction likely explains the increased incidence of left atrial enlargement.

On the basis of our results, we believe that atrial septal aneurysms and right-to-left shunting may be predictive of PFOs that predispose subjects to embolic infarcts. A PFO is unlikely to have precipitated an infarct without either or both of these factors. Most individuals with a PFO have alternatives causes for stroke that must be investigated before causality is assigned. Aspirin may be sufficient stroke prophylaxis for PFO-related infarcts after initial ischemia, reserving warfarin and surgical correction for those in whom aspirin is not effective or those who need warfarin or cardiac surgery for other reasons. A lengthy prospective study of subjects with PFO will be necessary to establish the relation of PFO and associated cardiac anomalies to stroke and to optimize medical or surgical infarct prophylaxis.

References
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Stroke. 1994;25:782-786
doi: 10.1161/01.STR.25.4.782

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