Surgical Patent Foramen Ovale Closure for Prevention of Paradoxical Embolism–Related Cerebrovascular Ischemic Events

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Background—The role of surgical closure of patent foramen ovale (PFO) for cerebral infarction (CI) or transient ischemic attack (TIA) resulting from paradoxical embolism is unclear, and its effect on recurrence is unknown. Our objective was to determine the outcome of surgical closure of PFO in patients with a prior ischemic neurological event, define the rate of CI or TIA recurrence after PFO closure, and identify risk factors for these recurrences.

Methods and Results—We retrospectively analyzed 91 patients (58 men, 33 women) with ≥1 previous cerebrovascular ischemic events who underwent surgical PFO closure between April 1982 and March 1998. The presence of a PFO with a right-to-left shunt was confirmed with transesophageal echocardiography. Mean age was 44.2 ± 12.2 years. The index event was a CI in 59 and a TIA in 32; a Valsalva-like episode preceded the event in 15 patients. Deep venous thrombosis was documented in 9 patients, and a hypercoagulable state was identified in 10. Surgical closure was performed with extracorporeal circulation by either direct suture (n=82) or patch closure (n=9). Limited incisions were used in 18.7% of patients. There was no operative mortality. Morbidity included transient atrial fibrillation (n=11), pericardial drainage for effusion (n=4), exploration for bleeding (n=3), and superficial wound infection (n=1). Follow-up totaled 176.3 patient-years, and mean follow-up was 2.0 years. No one had a CI, and 8 had a TIA during follow-up, with 1 caused by temporal arteritis. Transesophageal echocardiography demonstrated all closures to be intact in these patients. The overall freedom from TIA recurrence during follow-up was 92.5 ± 3.2% at 1 year and 83.4 ± 6.0% at 4 years. Having multiple neurological events before PFO closure was the only significant risk factor for TIA or CI recurrence after closure by univariate analysis (P=0.05); the small number of post-PFO closure cerebral ischemic events precluded multivariate analysis.

Conclusions—Surgical closure of PFO can be performed with minimal morbidity and mortality. PFO closure may decrease the risk of recurrent stroke or TIA and may avoid lifelong anticoagulation in the young adult if there is no other indication. Recurrent cerebrovascular ischemic events after surgery should prompt further evaluation to identify causes other than paradoxical embolism. (Circulation. 1999;100[suppl II]:II-171–II-175.)

Key Words: heart septal defects ■ stroke ■ embolism

Stroke causes >100 000 deaths in the United States each year and leaves many thousands of others with a major disability. In 25% to 40% of strokes in young adults, an extensive evaluation fails to identify the cause; they are classified as cryptogenic strokes. The role of a communication at the atrial level (patent foramen ovale [PFO] or atrial septal defect [ASD]) as a mechanism of paradoxical embolism and cerebral ischemic events has been recognized. The assumed mechanism for PFO-related systemic ischemic events is paradoxical embolism of venous thromboemboli. Several other cardiogenic embolic mechanisms have been emphasized as the cause of such strokes, including atrial and ventricular septal aneurysm and ascending aortic/arc atheroma. However, the diagnosis of a cardioembolic stroke remains presumptive and can seldom be proven.

Because the role of PFO in the mechanism of stroke in any individual patient may be unclear, treatment options can range from no therapy, to antiplatelet or anticoagulant therapy or both, to surgical PFO closure. The main advantage of PFO closure is that it provides a permanent closure of the defect, thereby preventing future paradoxical emboli without the added risks associated with long-term anticoagulation. The major disadvantage of surgical PFO closure is that it requires an operation. Despite the controversy, an increasing number of patients have been referred for operation in recent years.

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The purpose of this retrospective study was to define the risks of complications from surgical PFO closure. In addition, patients were followed up for recurrent neurological events, and attempts were made to identify risk factors associated with recurrence.

Methods

Patient Population
Between April 1982 and March 1998, 91 patients (58 men, 33 women) who had suffered a cerebral infarction (CI) or transient ischemic attack (TIA) underwent cardiac operation at our institution for interatrial communication closure for presumed paradoxical cerebral embolism. Two additional patients (total of 93) underwent PFO closure for preoperative neurological symptoms that were later found to be due to a disorder other than paradoxical embolism (glaucoma and spinal cord lesion); these patients were excluded from the analysis for CI/TIA recurrence. Patient medical records were abstracted to collect historical, clinical, radiographic, and trans-esophageal echocardiographic (TEE) characteristics. The mean age was 44.2 ± 12.2 years (range, 16 to 70 years). Patients who were operated on primarily for other cardiac reasons and had an incidental PFO diagnosed and closed at the time of operation were not included. Patients with other probable causes for a cardioembolic stroke such as atrial fibrillation, left atrial thrombi, or mitral valve disease were also excluded. For the purposes of this review, we defined a PFO as an interatrial communication with a right-to-left shunt only and an ASD as a defect that permitted bidirectional shunting. For simplicity, the term PFO will be used to include both in this article.

All the patients had a history of ≥1 cerebral ischemic episode before PFO closure. A CI was defined as an acute, focal neurological deficit lasting >24 hours with or without an abnormality in the corresponding cerebrovascular distribution noted on CT and/or MRI imaging. TIA was defined as the abrupt onset of focal neurological symptoms caused by localization brain ischemia resolving within 24 hours with or without a corresponding lesion on CT and/or MRI imaging. The initial, or index, neurological event was considered the event that prompted medical evaluation that identified the PFO. CI was the index event in 59 patients (65%), TIA in 31 (34%), and transient monocular blindness in 1 (1%). In 30 patients (33%), there was >1 cerebrovascular ischemic event before PFO closure; in 9 patients (10%), there were >2 neurological events before PFO closure. The index event was in the distribution of the anterior cerebral circulation in 73 patients (80%), posterior circulation in 17 (19%), and retinal in 1 (1%). The most frequent neurological symptom was upper extremity hemiparesis, which was present in 57 patients (63%).

In 90 patients, the presence of an interatrial communication with a right-to-left shunt was diagnosed with TEE. If no right-to-left shunt was seen initially, a Valsalva maneuver was performed. In the remaining 1 patient (from 1982), the diagnosis was made with angiography. In 75 patients (82%), there was a spontaneous right-to-left shunt; in 16 (18%), the right-to-left shunt was present only with a Valsalva maneuver. In 24 patients (26%), there was also left-to-right shunting present. One patient had a residual right-to-left shunt after prior patch closure of an ASD done elsewhere. An atrial septal aneurysm was found in addition to the interatrial communication in 17 patients. Qualitative assessment of the right-to-left shunt was made by TEE with agitated saline contrast. The mean size of the PFO defect by TEE was 5.4 ± 2.1 mm (range, 3 to 10 mm); the mean size of the ASD was 11 ± 5.9 mm (range, 5 to 25 mm). In all cases, the width of the stream of bubbles coming across the interatrial defect was at least equal to the size of the defect. All patients had normal cardiac functions and chamber sizes. There was no known intracardiac thrombus or ascending aortic atheroma, and all patients were in sinus rhythm.

Additional studies were obtained to rule out other causes of embolism. Duplex ultrasonographic study of the carotid arteries was performed in 42 patients and demonstrated no significant abnormal-

| TABLE 1. Hematological Survey Performed in 61 Patients at the Time of the Index Neurological Event |
|-------------------------------------------------|-------|--------|
| Anticardiolipin antibodies                       | 2     | 2.2    |
| Factor V Leiden mutation                        | 2     | 2.2    |
| Factor 12 deficiency                            | 1     | 1.1    |
| Plasminogen activator inhibitor deficiency      | 1     | 1.1    |
| Low activated protein C                         | 1     | 1.1    |
| Thrombocytosis                                  | 1     | 1.1    |
| Lupus anticoagulant                             | 2     | 2.2    |

Potential risk factors for paradoxical embolism at the time of the index event included smoking in 31 patients (34%), a Valsalva-like maneuver in 15 (16%), use of oral contraceptives in 10 (11%), a coagulation abnormality in 10 (11%), deep venous thrombosis in 9 (10%), and pregnancy and pulmonary embolism in 3 patients (3%) each. Additional comorbid medical conditions included treated hypertension in 13 patients (14%), non-insulin-dependent diabetes in 1, and insulin-dependent diabetes in 1. A history of a migraine type headache was present in 24 patients (26%). Four patients had a history of a long car ride or airplane flight before the event.

A hematological survey to identify a hypercoagulable state was obtained in 61 patients (67%). Ten patients were found to have an abnormality potentially consistent with a hypercoagulable state (Table 1).

The mean time interval between the index event and PFO closure was 1.6 ± 3.3 years. After the index neurological event, the patient’s physician advised treatment with warfarin in 59 patients (65%) and aspirin therapy in 77 (85%). Subsequently, 30 patients had a second neurological event; 18 were on warfarin therapy and 8 were on aspirin therapy.

Follow-Up
Patient data were collected from medical records. Each patient was also interviewed for any postoperative neurological symptoms with the use of a standardized telephone questionnaire. A recurrent event was defined as any neurological event consistent with a CI or TIA as determined by a physician after PFO closure. Postoperative follow-up was available in 100% of the patients.

Statistical Analysis
Clinical and demographic variables were summarized by mean and SD for continuous variables and as frequency for categorical variables. Kaplan-Meier estimates of freedom from recurrent ischemic events after PFO closure were constructed, and the influence of each independent variable (age, sex, smoking, presence of a Valsalva-like maneuver before index event, location of the index event, presence of a recurrence before closure, drug therapy after surgery) was analyzed with the log-rank test or Cox proportional-hazard models. Ninety-five percent confidence intervals were calculated for survival estimates. Significance was assumed at P < 0.05.

Results
All patients underwent standard cardiac surgical techniques with cardiopulmonary bypass and cardioplegic arrest. The surgical approach was a median sternotomy in 74 patients (81%), a limited right thoracotomy in 6 (6.6%), and an
inferior “mini-sternotomy” in 11 (12%). Atrial septal plication or resection was performed in 15 patients (16%). The defect was closed primarily in 82 patients and with an autologous pericardial patch in 9 patients. The mean size of the interatrial defect was 8.4±5.3 mm (range, 3 to 30 mm) as noted by the operating surgeon. Additional procedures were performed in a total of 10 patients: coronary artery bypass grafting in 5; ligation of the left atrial appendage in 2; and pulmonary valvotomy, mitral valve exploration, and tricuspid valve repair in 1 each. Mean cardiopulmonary bypass time was 36±21 minutes (range, 12 to 154 minutes), and mean aortic occlusion time was 18±14 minutes (range, 5 to 101 minutes). An intraoperative TEE was performed to confirm closure of the defect and to document no residual shunt across the atrial septum in all but 1 patient, who was operated on in 1982. That patient subsequently underwent TEE in later years that documented closure of the defect.

There was no operative mortality after surgical PFO closure. Morbidity included atrial fibrillation in 11 patients (11%); 6 were converted to sinus rhythm with digoxin and β-blockers, and 4 patients required electrical cardioversion. All but 1 patient was in sinus rhythm 30 days after surgery. That patient underwent a catheter ablation of the AV node and permanent pacemaker implantation. A pericardial effusion occurred in 6 patients (6.6%), and 4 patients required echo-guided percutaneous drainage of the effusion. Pericardial effusion occurred in 5 of 82 patients receiving warfarin and/or aspirin therapy postoperatively compared with 1 of 9 patients not those therapies (P=0.5). Three patients required exploration for postoperative bleeding (3.3%). One patient had a superficial sternal wound infection that was successfully treated with local wound care and antibiotic therapy. One patient had an asymptomatic sternal nonunion. There was no perioperative stroke, myocardial infarction, or episode of hemodynamic instability. All patients were extubated within 24 hours of operation, and 88 (97%) were dismissed from the intensive care unit the day after surgery; 2 were dismissed within 48 hours of operation, and 1 was dismissed 72 hours after surgery. The mean hospital stay was 5.7±3.0 days (range, 3 to 24 days). Postoperatively, oral anticoagulation therapy with warfarin was prescribed in 49 patients (62%). Further antiplatelet or anticoagulant therapy was determined at the discretion of the primary physician.

**Follow-Up**

Total follow-up was 176.3 patient-years; the mean follow-up was 1.9±2.2 years (maximum, 11.4 years). One patient died at 63 years of age because of an acute myocardial infarction 11 years after PFO closure. At late follow-up, 6 patients (7%) were on warfarin therapy alone, 33 patients (36%) were on aspirin therapy alone, and 5 (5%) were on warfarin and aspirin therapy. Among the 90 survivors, 8 patients had recurrent cerebrovascular ischemic symptoms, all consistent with TIAs. One of the 8 with symptoms (transient monocular blindness) had temporal arteritis as the probable cause (Table 2). There was no recurrence in the patient who required an AV node ablation and permanent pacemaker placement. Univariate analysis demonstrated multiple cerebrovascular ischemic events before PFO closure to be a risk factor for a neurological event occurring after PFO closure (P=0.05) (Table 3). The small number of cerebral ischemic events that occurred after PFO closure precluded a multivariate analysis. Freedom from a recurrent cerebral or retinal ischemic event for all patients was 92.5±3.2% at 1 year and 83.4±6.0% at 4 years (the Figure).

### TABLE 2. Recurrent Neurological Events After PFO Closure

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Sex</th>
<th>Initial Problem</th>
<th>Operation Year</th>
<th>Recurrence</th>
<th>Recurrence Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>F</td>
<td>UEH, LEH, FD</td>
<td>1989</td>
<td>Gait disturbance</td>
<td>1991</td>
</tr>
<tr>
<td>40</td>
<td>F</td>
<td>Dysarthria</td>
<td>1996</td>
<td>Same</td>
<td>1996</td>
</tr>
<tr>
<td>42</td>
<td>M</td>
<td>UEH, LEH, aphasia</td>
<td>1996</td>
<td>Confusion, stereotactic spells</td>
<td>1997</td>
</tr>
<tr>
<td>45</td>
<td>M</td>
<td>UEH, dysarthria</td>
<td>1994</td>
<td>Dysarthria</td>
<td>1995</td>
</tr>
<tr>
<td>51</td>
<td>M</td>
<td>UEH, FD, visual disturbance</td>
<td>1995</td>
<td>UEH, paresthesia</td>
<td>1997</td>
</tr>
<tr>
<td>62</td>
<td>M</td>
<td>Gait and visual disturbance, confusion</td>
<td>1998</td>
<td>TMB</td>
<td>1998</td>
</tr>
<tr>
<td>62</td>
<td>M</td>
<td>Gait and visual disturbance, confusion</td>
<td>1996</td>
<td>Visual disturbance</td>
<td>1997</td>
</tr>
<tr>
<td>63</td>
<td>M</td>
<td>UEH, LEH, FD, gait and visual disturbance</td>
<td>1996</td>
<td>Visual disturbance, dysarthria, confusion</td>
<td>1996</td>
</tr>
</tbody>
</table>

UEH indicates upper extremity hemiparesis; LEH, lower extremity hemiparesis; FD, facial drop; and TMB, transient monocular blindness.

### TABLE 3. Kaplan-Meier Log Rank for Recurrent Neurological Events After PFO Closure

<table>
<thead>
<tr>
<th>Variable</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events, 1 vs &gt;1</td>
<td>0.05</td>
</tr>
<tr>
<td>Valsalva maneuver</td>
<td>0.2</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.9</td>
</tr>
<tr>
<td>Index event, stroke vs TIA</td>
<td>0.5</td>
</tr>
<tr>
<td>Migraine</td>
<td>0.7</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.8</td>
</tr>
<tr>
<td>CNS distribution, anterior vs posterior</td>
<td>0.9</td>
</tr>
<tr>
<td>Age, &lt;55 vs ≥55</td>
<td>0.1</td>
</tr>
<tr>
<td>Hypercoagulable state</td>
<td>0.3</td>
</tr>
</tbody>
</table>

CNS indicates central nervous system.
Discussion

The relationship between cryptogenic stroke in young patients and the presence of a PFO was first demonstrated by case-control studies in late 1980s. These studies demonstrated that in patients <60 years of age with a stroke of unknown cause, a PFO was present in 40% to 50% compared with a 10% to 15% incidence in control subjects. More recent studies have identified PFO and atrial septal aneurysm as risk factors for recurrence in patients with stroke. In the study reported by Mas and Zuber, the actuarial risk of having a recurrent stroke at 2 years was 2.3%; the risk of stroke or TIA was 6.7% in patients <60 years of age with a stroke and PFO with or without an atrial septal aneurysm. In another study, Bogousslavsky et al followed 140 patients with stroke and PFO for 3 years and observed a recurrent stroke or death rate of 2.4%/y. They showed that the presence of an interatrial communication was a significant risk factor for recurrence by multivariate analysis.

Despite the growing interest in PFO and atrial septal aneurysm as a risk factor for paradoxical embolism–induced neurological events, there is still no consensus on the optimal treatment. Currently, there are 4 basic treatment options: no treatment, antiplatelet therapy with aspirin, anticoagulation with warfarin, or invasive closure of the PFO. Nendaz et al have shown recently that in a hypothetical cohort of young patients with stroke analyzed within a wide range of stroke risk recurrence (0.8%/y to 7%/y), the benefit obtained by PFO closure exceeded that of other therapeutic options. Compared with abstaining from treatment, antiplatelet therapy was beneficial when the risk of CI was >0.8%/y, and anticoagulation was beneficial when it was >1.4%/y. Using their model, they suggest that PFO closure and long-term anticoagulation appear to represent the best choices for selected patients according to age, risk of stroke recurrence, tolerance for anticoagulants, and immediate procedure risk.6

Although surgical closure of an interatrial communication without the use of a foreign body has been definitive and the gold standard, closure of a PFO can be accomplished with transcatheter techniques. Bridges et al reported closure of PFO for stroke prevention in 36 patients with the double-umbrella device with no complications, but at follow-up, several patients had residual shunts across the atrial septum. Currently, various devices are being evaluated for catheter-based PFO or ASD closure. Although sufficient data have been collected to indicate that transcatheter ASD closure is a viable alternative to surgery in selected patients, none of these devices has been approved yet for widespread clinical use. In a recent review, Nendaz et al considered surgical closure the gold standard for future procedures.

Surgical closure of PFO with or without aspirin for the prevention of stroke recurrence has been reported from various centers. In all reported studies, there was no early mortality. Guffi et al reported on 11 patients with a mean age of 39 years and a mean follow-up of 12.2 months, and Devuyst et al reported on 30 patients with a mean age of 38 years and a mean follow-up of 2 years. In both studies, there was no stroke recurrence. On the other hand, Homma et al reported on 28 patients with a mean age 41 years who were followed for a mean of 19 months; they observed 5 recurrences with an actuarial rate of recurrence of 19.5%. The recurrences were significantly more frequent in older patients (relative risk for recurrence, 2.76 per 10 years). They also reported an incidence of 18% of postpericardiotomy syndrome.

In our retrospective study of 91 patients, there was also no hospital mortality. We documented recurrent neurological ischemic symptoms in 8 patients; in all patients, the recurrence was a TIA and not a CI. In 1 patient, a definitive diagnosis other than cardioembolic ischemia (temporal arteritis) was made at the time of the recurrent neurological event. Because we have been able to document PFO closure by TEE
in all patients, it is likely that these recurrences were due to causes other than paradoxical embolism. Multiple neurological events before PFO closure were marginally significant for recurrence after PFO closure ($P=0.05$), and there were too few events after PFO closure to perform a multivariate analysis. This finding could be explained if most of the patients with multiple events had preoperative recurrences in the same vascular distribution as the first event, making it plausible that the mechanism for their symptoms was distal arterial occlusive disease, not defined on neuroimaging studies. The arterial distribution of the preoperative recurrences was not available for the patients in this study. The finding that older age ($\geq 55$ years) was not a significant risk factor for recurrence may be due to the relatively small number of patients $>55$ years of age ($n=20$). It is interesting to note that none of the recurrences were in patients who had a Valsalva-like maneuver preceding the index event.

One patient operated on for a presumed diagnosis of retinal emboli (transient monocular blindness) had recurrences of the same symptoms after PFO closure. Further evaluation demonstrated a different diagnosis (temporal arteritis). This finding has prompted us to consider and evaluate patients more thoroughly with PFO and isolated visual symptoms before advising PFO closure. Although treatment of patients with a hypercoagulable state is directed at the underlying coagulation defect and usually includes warfarin therapy with or without aspirin, our approach has been to selectively recommend PFO closure in addition to appropriate anticoagulation, especially in the young patient.

The most frequent morbidity was atrial fibrillation, but the most common complication requiring intervention was pericardial effusion that necessitated percutaneous echo-guided drainage in 4 patients. This may be related to postoperative anticoagulation used in a large number of patients because the incidence of effusion was higher in anticoagulated patients. Although there is no unanimous consensus at our institution, our general approach for patients in normal sinus rhythm has been to advise warfarin or aspirin therapy for 6 to 8 weeks postoperatively; any further anticoagulation or antiplatelet therapy is then left to the discretion of the primary physician. Following recent trends, an increasing number of cardiac surgical procedures have been performed with more cosmetic surgical incisions (limited sternotomy and limited thoracotomy), which have not increased the risk of the procedure.

In our experience, the main issue with CI, especially in young patients, relates to the uncertainty of the cause and diagnosis. The incidence of a PFO with right-to-left shunting during Valsalva maneuvers approaches 20% in the general population. It is reasonable to assume that in some patients who have a PFO with stroke or TIA of unknown cause despite comprehensive evaluation, the mechanism for stroke may be paradoxical embolism. Nevertheless, invasive closure of the PFO would be unnecessary and inappropriate when other compelling causes are present, as seen in our series and shown by others. However, the risks of long-term anticoagulant therapy have been well documented and can significantly alter day-to-day quality of life, especially in the young adult. Surgical treatment offers permanent closure of the defect with minimal risk and avoids long-term anticoagulation and its associated complications. Increasing recognition of the role of PFO in CI at our institution has led to an increasing number of the procedures being performed. The results of this large surgical series can be used as a reference for future evaluation of transcatheter closure devices. The degree to which PFO closure reduces the recurrence of cerebrovascular ischemic events needs to be defined with a controlled study.

Acknowledgment

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