Percutaneous Transcatheter Closure of Patent Foramen Ovale in Patients With Paradoxical Embolism

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Background—Percutaneous transcatheter closure of patent foramen ovale (PFO) is used as an alternative to surgery or long-term anticoagulation for the treatment of patients with paradoxical embolism and PFO.

Methods and Results—We report the immediate and long-term clinical and echocardiographic outcome of 110 consecutive patients (58 males, mean age 47 ± 14 years) who underwent transcatheter closure of PFO because of paradoxical embolism between 1995 and 2001. Procedural success, defined as successful deployment of the device and effective occlusion (no, or trivial, shunt after device placement), was achieved in all (100%) patients. There was no in-hospital mortality, 1 device migration requiring surgical intervention (0.9%), and 1 episode of cardiac tamponade (0.9%) requiring pericardiocentesis. A progressive increment in full occlusion was observed (44%, 51%, 66%, and 71% at 1 day, 6 months, and 1 and 2 years, respectively, after device placement). At a mean follow-up of 2.3 years, 2 patients experienced recurrent neurological events (1 fatal stroke and 1 transient ischemic attack), representing an annual risk of recurrence of 0.9%. In addition, 4 (3.6%) of the patients required reintervention for device malalignment or significant shunt. Kaplan-Meier analysis showed a freedom from recurrent embolic events and reintervention of 96% and 90% at 1 and 5 years, respectively.

Conclusions—Transcatheter closure of PFO is a safe and effective therapy for patients with paradoxical embolism and PFO. It is associated with a high success rate, low incidence of hospital complications, and low frequency of recurrent systemic embolic events. (Circulation. 2002;106:1121-1126.)

Key Words: heart septal defects ■ embolism ■ catheterization ■ stroke

Patent foramen ovale (PFO) has been identified as a source of paradoxical embolism. Frequent forms of presentation of paradoxical embolism include cryptogenic stroke,1–4 peripheral embolism,3,5 brain abscess,6 and decompression sickness in underwater divers.4,7,8 Although the underlying mechanism whereby PFO accounts for this phenomenon is unknown, it is thought to involve the passage of emboli from the right- to the left-sided cardiac chambers through the PFO.9,10 Patients with PFO and paradoxical embolism are at increased risk of recurrent systemic thromboembolic events, ranging from 3.2% to 3.8% per year.11–14 The optimal management of these patients remains controversial. Long-term anticoagulation,11,12,15 surgical PFO closure,16–18 and percutaneous transcatheter closure of the PFO19–21 have been proposed as therapeutic options. Oral anticoagulation and surgical closure are associated with a significant morbidity and mixed results regarding stroke prevention.11,12,15–18 Transcatheter techniques to close PFO have been used with increasing frequency during the last few years. The present study prospectively assessed the immediate and long-term clinical and echocardiographic follow-up of 110 consecutive patients with paradoxical embolism who underwent percutaneous PFO closure at Massachusetts General Hospital.

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Methods

Patient Population

The patient population included 110 patients with PFO and ≥1 paradoxical embolic event who underwent percutaneous transcatheter closure of PFO at the Massachusetts General Hospital between January 1995 and September 2001. All patients underwent a thorough and rigorous evaluation to rule out other causes of systemic emboli. The diagnosis of paradoxical embolism was established when a PFO was identified by 2D or tranesophageal echocardiography (TEE) and there was no other identifiable cause of systemic embolism. Patients’ evaluations varied but included the following: neurological examination, brain CT, extracranial Doppler ultrasonography, brain MRI, and in selected cases cerebral angiography, 12-lead ECG, 24- and 48-hour Holter monitoring, 2D echocardiog-
raphy with microbubble test with and without the Valsalva maneuver, TEE, standard blood tests and hypercoagulable workups (proteins C and S, antithrombin III, lupus anticoagulant, anticardiolipin antibodies, homocysteine, and factor V Leiden), Doppler and phlebography of lower extremities to rule out deep vein thrombosis, pelvic magnetic resonance venous imaging, and pulmonary ventilation/perfusion (V/Q) scan (in cases suspected of pulmonary embolism).

Procedure
Closure of the PFO was performed by using either buttoned devices (Sideris) or CardioSEAL occluder devices (NMT Medical, Inc), as previously described.\(^1\) The Sideris buttoned device was implanted in patients with paradoxical embolism and a PFO as part of a multicenter trial approved by both the US Food and Drug Administration and the Massachusetts General Hospital Investigational Review Board. The CardioSEAL device was used after approval of this device under humanitarian device exemption by the US Food and Drug Administration and establishment of a registry approved by the Massachusetts General Hospital Investigational Review Board. This registry included patients with warfarin allergy, paradoxical embolism, with recurrent paradoxical embolism while on warfarin therapy, and patients at high risk for warfarin therapy. PFO closure was undertaken under general anesthesia with TEE and fluoroscopy guidance. Patients received cefazolin (1 g IV) at the time of the procedure, followed by 1 g intravenously every 8 hours for an additional 2 doses. Vancomycin (1 g IV) at the time of the procedure, followed by an additional dose 12 hours later, was used in patients allergic to penicillin. Patients were systemically anticoagulated at the time of the procedure with intravenous heparin (70 to 100 U/kg). Before device implantation, the patients underwent percutaneous diagnostic cardiac catheterization from the right femoral artery and right femoral vein. Hemodynamic and oxygen saturation measurements were performed. A 7F Goodale Lubin catheter was used to cross from the right atrium into the left atrium across the PFO. The catheter was then advanced into the right upper pulmonary vein and exchanged for a 5.5F pigtail catheter with 1-cm radiopaque markers over a 0.035-in Amplatz exchange guidewire. Right upper pulmonary vein angiography was performed in the left anterior oblique projection with cranial angulation. Subsequently, the Amplatz exchange guidewire was placed into one of the left pulmonary veins, and the pigtail catheter was removed. A sizing balloon catheter was advanced over the guidewire, and stretched balloon sizing of the PFO was performed by angiography and TEE. The sizing balloon was then removed. A 10F or 11F Mullins’ sheath was placed in the left upper pulmonary vein over the Amplatz guidewire. A closure device with a device diameter/PFO stretched diameter ratio of ≥2 was chosen, advanced through the Mullins’ sheath, and deployed under angiographic and TEE guidance. Optimal placement of the device was assured by TEE and by the presence of none or minimal shunt after deployment by color flow Doppler and microbubble administration. The device was released, and right atrium angiography with follow-through was performed in the left anterior oblique projection with cranial angulation. Two-dimensional echocardiography, chest x-ray, and ECG were repeated 24 hours after the procedure and before hospital discharge. Patients were discharged on aspirin (325 mg daily) and subacut bacterial endocarditis prophylaxis for 6 months. In patients with aspirin allergy, clopidogrel (75 mg daily) or ticlopidine (250-mg twice daily) was prescribed. Patients requiring short- or long-term anticoagulation with warfarin for other causes, such as patients with venous or arterial hypercoagulable states, deep venous thrombosis, and pulmonary embolism, were discharged on low molecular weight heparin while undergoing warfarin loading. Patients with a hypercoagulable state, with 1 clot and a risk factor for clotting that could be eliminated, received 3 to 4 months of warfarin anticoagulation after device placement and were switched to aspirin thereafter. Patients with a hypercoagulable state and ≥2 clots and those with an arterial hypercoagulable state regardless of the presence of an associated risk factor for clotting at the time of paradoxical embolism were prescribed life-long warfarin anticoagulation.

Follow-Up Evaluation
Patients were followed clinically and echocardiographically at 24 hours, 1 month, 6 months, and 12 months after device implantation and yearly thereafter. Follow-up information was obtained by periodic visits with physicians. When necessary, local physicians were contacted for further information, and medical records were reviewed. Echocardiographic examinations were reviewed and assessed for the presence of residual shunt. Residual shunt was determined by 2D echocardiography, color flow Doppler, and agitated saline solution contrast injection into an antecubital vein and categorized as follows: 0, none, indicating no microbubbles in the left atrium after administration of agitated saline; 1, small, indicating the presence of 3 to 9 microbubbles in the left atrium after the administration of agitated saline; 2, moderate, indicating 10 to 30 microbubbles in the left atrium after administration of agitated saline; and 3, large, >30 microbubbles in the left atrium after administration of agitated saline.\(^2\)

Follow-up events included death, recurrent neurological or peripheral thromboembolic events, and the need of intervention for significant residual shunt or device malalignment. A recurrent embolic event was established by neurological evaluation by a specialist and confirmed when necessary by the appropriate imaging studies (MRI, CT, and angiography).

Statistical Analysis
All data were entered into a computerized database that was specifically designed for the present study. Data are presented as mean±SD, and values of \(P<0.05\) were considered significant. Kaplan-Meier estimates were used to determine total survival, survival with freedom from recurrent embolic events, and survival with freedom from recurrent thromboembolic events and reintervention. Actuarial risk of recurrent embolic events at mean follow-up was determined by using the Kaplan-Meier life-table analysis method. The annual risk of recurrence (\(R_{\text{annual}}\)) was calculated from the actuarial risk (\(R_{\text{actuarial}}\)) by the following formula: \(R_{\text{annual}} = 1-(1-R_{\text{actuarial}})^{\text{days}}\). The log-rank test was used to compare the rate of recurrence between patients with and without atrial septal aneurysm. All analyses were performed by using SPSS software (version 10.0, SPSS Inc).

Results
Patient Population
The patient population included 110 consecutive patients with a history of \(\geq 1\) presumed paradoxical embolism who underwent transcatheter closure of the PFO. Baseline characteristics of the patient population are shown in Table 1. There were 58 (53%) males and 52 (47%) females with a mean age of 47±14 (range 14 to 77) years. Indications for PFO closure included ischemic neurological event in 105 patients (2 of them had also platypnea/orthodeoxia syndrome), other peripheral embolism in 2 patients (one splenic and another in the left femoral artery), and brain abscess in 3 patients. A concomitant pulmonary embolism occurred in 2 patients. Multiple paradoxical embolisms occurred in 27 (25%) patients, yielding an average of 1.4±0.7 embolic events per patient. Seventeen patients had 2 embolic events, 8 patients had 3 embolic events, and 2 patients had 4 embolic events. Our PFO cohort of patients is a high-risk population for recurrent embolic events as reflected by the following: 25% incidence of previous multiple embolic events, 14% incidence of atrial septal aneurysm, 16% incidence of atrial septum hypermobility, 71% presence of spontaneous right to left shunt through the PFO, and 11% incidence of hypercoagulable state.
Procedural Results

The PFO stretched diameter assessed by both angiography and TEE was 11.4 mm. PFO closure was performed by using the buttoned device in 77 patients and by using the CardioSEAL device in 33 patients (Table 2). The average device size was 28.6 mm, resulting in a device size/PFO stretched diameter size ratio of 2.8 ± 0.9. Successful device implantation was accomplished in 110 (100%) of the patients. Effective occlusion (no shunt or small residual shunt) was present in all patients immediately after device deployment. Full occlusion was present in 49 (45%) of the patients, and a trivial shunt was present in 61 (55%) of the patients. In 8 patients, a second device was needed to accomplish effective PFO closure. At 24 hours after device placement, full occlusion was present in 48% of the patients, small shunt was present in 49% of the patients, mild shunt was present in 2% of the patients, and moderate shunt was present in 1% of the patients (Figure 1).

In-Hospital Complications

There were no deaths or systemic thromboembolic events. Migration of a buttoned device to the pulmonary artery occurred in 1 patient within 30 minutes after device placement, requiring immediate surgical intervention for device removal and closure of the PFO. One patient developed an episode of cardiac tamponade within 24 hours after the procedure, requiring pericardiocentesis. During the procedure, 1 (2%) of the patients developed atrial fibrillation, which converted spontaneously to normal sinus rhythm, and 1 patient developed an episode of supraventricular tachycardia successfully treated with adenosine (Table 3).

Follow-Up

The mean follow-up was 2.3 ± 1.7 years. There were 3 deaths. One patient died from recurrent multiple strokes 3 weeks after PFO closure. The autopsy showed an intact and well-placed device. There was evidence of metastatic pulmonary adenocarcinoma to lungs, heart, liver, and lymph nodes and multiple occlusive blood clots resulting in cortical, subcortical, and cerebellar infarcts. In addition, a subacute myocardial infarct with acute extension and left ventricular mural thrombosis was also present. One patient died from end-stage renal failure.

Table 1. Patient Population

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>110</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>47±14</td>
</tr>
<tr>
<td>Females</td>
<td>52 (47)</td>
</tr>
<tr>
<td>Males</td>
<td>58 (53)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (16)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>29 (26)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>22 (20)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Multiple neurological events</td>
<td>27 (25)</td>
</tr>
</tbody>
</table>

Table 2. Procedural Data

<table>
<thead>
<tr>
<th>Procedural success</th>
<th>110 (100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFO-stretched diameter, mm</td>
<td>11±4</td>
</tr>
<tr>
<td>Device size, mm</td>
<td>28±6</td>
</tr>
<tr>
<td>Device size/PFO stretched diameter size ratio</td>
<td>2.8±0.9</td>
</tr>
<tr>
<td>Need for second device</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Immediate residual shunt</td>
<td>None residual shunt 49 (44.5)</td>
</tr>
<tr>
<td>Small shunt</td>
<td>61 (55.5)</td>
</tr>
<tr>
<td>Moderate shunt</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Large shunt</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fluoroscopy time, min</td>
<td>18±9</td>
</tr>
</tbody>
</table>

Table 3. In-Hospital Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Device migration</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Emergency surgery*</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Percutaneous tamponade</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Values are n (%). *Same patient with device migration.
failure, and 1 patient died from pulmonary fat embolism after a hip fracture.

Recurrent Systemic Embolic Events
There were 2 recurrent neurological events. First, a fatal stroke occurred in a 74-year-old man 3 weeks after device placement, as described above. Second, a recurrent transient ischemic attack (TIA) occurred in a 64-year-old female 10 months after device implantation. Both patients had no residual shunt and correct device position in recent echocardiographic studies. Furthermore, neither of them had a hypercoagulable state. Kaplan-Meier analysis revealed an actuarial risk of recurrent embolic events of 2.1% at 5-year follow-up (Figure 2A). Of note, the 2 recurrent embolic events occurred within the first year of follow-up.

Reintervention
A total of 4 patients required reintervention for significant residual shunt or device malalignment, resulting in a 98% and 92% actuarial freedom from reintervention at 1 and 5 years, respectively (Figure 2B). Three patients were treated surgically, and 1 patient was treated by percutaneous placement of another device. The first patient had surgery because of early migration of the device to the left main pulmonary artery, as described above. Two patients underwent cardiac surgery because of late device malalignment at 8 months and 3 years after device implantation. The last patient underwent successful repeat transcatheter closure 2 years after successful device implantation because of late development of device malalignment and significant bidirectional shunting. The 3 late device malalignments described above occurred in patients with Sideris buttoned devices, and no strut fractures were identified in any case.

The actuarial freedom from combined end point (reintervention and recurrent systemic thromboembolic event) was 96% and 90% at 1 and 5 years, respectively (Figure 2C).

Residual Shunt at Follow-Up
Follow-up echocardiography showed a progressive increase in the number of patients with full occlusion during the first year of follow-up (Figure 1). Full occlusion was present in 51% and 66% of the patients at 6- and 12-month follow-up, respectively. A small shunt was present in 47% and 33% of the patients at 6- and 12-month follow-up, respectively. Finally, a moderate shunt was present in 2 patients at 6 months of follow-up and in 1 patient at 1 year of follow-up. One patient developed significant shunt and device malalignment 2 years after successful closure and underwent successful repeat transcatheter closure, as described above.

Discussion
The present study demonstrates that transcatheter closure of PFO is a safe and effective technique for patients presenting with paradoxical embolism. This technique is associated with a high success rate, low incidence of procedural and in-hospital complications, and excellent long-term follow-up results.

The role of a PFO as a mechanism of paradoxical embolism and cerebral ischemic events has been recognized.
antiplatelet or anticoagulant therapy or both to surgical or transcatheter PFO closure.

Mas et al\textsuperscript{13} reported an average annual recurrence rate of 3.4\% for the combined end point of TIA and stroke in 132 patients treated with either aspirin or oral anticoagulation at a mean follow-up period of 1.9 years. An annual recurrence rate of 3.8\% was reported in the Lausanne Stroke Registry at the 3-year follow-up, with no significant difference between aspirin and oral anticoagulation.\textsuperscript{14} Risks of fatal hemorrhagic events between 2\% and 7\% and of major hemorrhagic events between 2.1\% and 12.8\% have been reported in patients with cerebrovascular disease treated with oral anticoagulation.\textsuperscript{23–25}

Mixed results of surgical closure of PFO in patients with paradoxical embolism have been reported. Dearani et al.\textsuperscript{26} reported their results in 91 patients with cryptogenic stroke who underwent surgical closure of a PFO. Although they had no operative mortality, atrial fibrillation occurred in 11 patients, and pericardial effusion occurred in 6 patients, with 4 of them requiring pericardiocentesis. Furthermore, 8 patients had recurrent TIAs, resulting in a freedom from recurrent neurological event of 92.5\% at 1 year and 83.4\% at 4 years. The results of Dearani et al are in contrast with those of Ruchat et al.,\textsuperscript{18} who reported 1 perioperative TIA and no further embolic events at a mean follow-up of 36 months in a series of 59 patients.

Transcatheter closure of PFO offers the advantages of closure of the defect without the disadvantages of open-heart surgery. In the present study, the atrial septal closure device was successfully deployed in all patients, and an effective occlusion (none or trivial shunt) was achieved in 100\% of patients. Procedural and in-hospital complications were low, as reflected in no deaths and no systemic thromboembolic events during hospitalization. We had 1 device embolization and 1 episode of pericardial tamponade requiring pericardiocentesis.

The present study demonstrated that at long-term follow-up, the incidence of recurrent embolic events was low. Recurrent embolic events occurred in only 2.1\% of the patient population at the 5-year follow-up, as shown in Figure 2A. The annualized risk for recurrent systemic thromboembolic events was 0.9\% at a mean follow-up period of 2.3 years (257 patient-years). Recurrent events occurred within the first 10 months of follow-up. This observation is in agreement with previous studies showing that the greater number of recurrences occur within the first year after device implantation.\textsuperscript{21} Thus, it is possible that a more intensive antiplatelet regimen and/or warfarin anticoagulation may be necessary during the first year after device placement before there is complete reendothelialization of the device. This approach is particularly important in patients with hypercoagulable states. Anticoagulation should be prolonged or permanent in arterial hypercoagulable states (ie, lupus anticoagulant and/or antiphospholipid antibody if the antibody persists) and in venous hypercoagulable states (hereditary risk factor) if the clotting has been recurrent or spontaneous in the absence of an identifiable risk factor.

In addition, the present study also showed that the incidence of residual shunt after device placement decreased during the follow-up period and that the need for surgical or catheter-based intervention for device malalignment or significant shunt was low. These findings are reflected in 96\% and 90\% freedom from systemic embolic event and reintervention at 1- and 5-year follow-up, respectively (Figure 2C). Although the device was deployed successfully in all patients at the time of the procedure, 3 of the 4 patients requiring surgical or repeat catheter intervention for significant shunt at follow-up had developed late device malalignment.

The presence of an atrial septal aneurysm has been identified by some investigators as an important factor associated with increased risk of neurological events.\textsuperscript{13,22,27–29} A 4.4\% per year rate of recurrent events was reported by Mas et al\textsuperscript{13} in patients with both PFO and atrial septal aneurysm treated with aspirin or oral anticoagulants. We found that after PFO device closure, the presence of atrial septal aneurysm is not associated with an increased incidence of recurrent embolic events (Figure 3). This finding is in agreement with those of Windecker et al\textsuperscript{21} and supports the results of Mas et al, ie, that in the absence of a patent foramen ovale, the presence of atrial septal aneurysm alone is not associated with an increased incidence of recurrent embolic events.\textsuperscript{22}

**Comparison With Previous Studies of Percutaneous Transcatheter Closure of PFO**

Bridges et al\textsuperscript{30} reported their results with transcatheter closure of the PFO in 36 patients with a mean age of 39 years. Successful device placement was achieved in all patients, and complete closure was accomplished in 29 (78\%). No recurrent thromboembolic events were observed at a mean follow-up of 8 months.

Only 1 of 46 patients suffered a recurrent TIA in a multicenter European study using the atrial septal defect occlusion system device for transcatheter PFO closure.\textsuperscript{31}

Hung et al\textsuperscript{20} reported the results of PFO transcatheter closure in 67 patients with a mean age of 46 years. An 86\% effective occlusion rate and a risk of recurrent stroke or TIA of 3.2\% per year were described at a mean follow-up of 2.6 years.

Windecker et al\textsuperscript{21} reported their experience of percutaneous PFO closure in 80 patients with a mean age of 52 years.
Implantation procedure was successful in 78 (98%) of the patients, and complete closure assessed by echocardiography was achieved in 57 (73%) of the patients. They reported a 10% incidence of in-hospital complications. At a mean follow-up at 1.6 years, there were 8 recurrent thromboembolic events (6 TIA’s and 2 peripheral emboli), resulting in an annual recurrence rate of 3.4%.

Our results compare favorably with those obtained with long-term oral anticoagulation and surgical or percutaneous closure of PFO for patients with paradoxical emboli. We achieved successful device implantation and effective occlusion in all patients. We had no in-hospital mortality, minimal in-hospital morbidity, and 0.9% risk of recurrent systemic embolic events per year at a mean follow-up of 2.3 years. The learning curve, technical improvements, and patient selection may account for these differences.

Limitations of the Study
We acknowledge some limitations of the present study. First, our patient population was a selected cohort referred to our center for percutaneous PFO closure and might differ from other series published. Second, the small number of recurrent events underpowered the present study to identify predictors of recurrent events or reintervention after device implantation. Because the incidence of recurrent embolic events was low, longer-term results are necessary before drawing final conclusions.

Conclusions
Transcatheter closure of PFO is an effective therapy for patients with paradoxical embolism and PFO. It is associated with a high success rate, a low incidence of hospital complications, and a low frequency of recurrent systemic thromboembolic events.

Acknowledgments
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References
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