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OBJECTIVES
We report the largest and the longest follow-up to date of patients who underwent transcatheter patent foramen ovale (PFO) closure for paradoxical embolism.

BACKGROUND
Closure of a PFO has been proposed as an alternative to anticoagulation in patients with presumed paradoxical emboli.

METHODS
Data were collected for patients following PFO closure with the Clamshell, CardioSEAL or Buttoned Devices at two institutions.

RESULTS
There were 63 patients (46 ± 18 years) with a follow-up of 2.6 ± 2.4 years. Fifty-four (86%) had effective closure of the foramen ovale (trivial or no residual shunt by echocardiography) while seven (11%) had moderate residual shunting. There were four deaths (leukemia, pulmonary embolism, sepsis following a hip fracture and lung cancer). There were four recurrent embolic neurological events following device placement: one stroke and three transient events. The stroke occurred in a 56-year-old patient six months following device placement. A follow-up transesophageal echocardiogram showed a well seated device without residual shunting. Two of the four events were associated with suboptimal device performance (one patient had a significant residual shunt and a second patient had a "friction lesion" in the left atrial wall associated with a displaced fractured device arm). The risk of recurrent stroke or transient neurological event following device placement was 3.2% per year for all patients.

CONCLUSION
Transcatheter closure of PFO is an alternative therapy for paradoxical emboli in selected patients. Improved device performance may reduce the risk of recurrent neurological events. Further studies are needed to identify patients most likely to benefit from this intervention.

The association of patent foramen ovale (PFO) and cerebrovascular events in selected patients is becoming increasingly established (1–7), with the underlying mechanism thought to be passage of emboli through the foramen (8–12). This association appears to be particularly strong in young patients with stroke (3,13). To our knowledge, the most appropriate therapy to prevent future embolic cerebrovascular events in patients with PFO has not been established (14–16). Anticoagulation and surgical closure have been proposed as measures to prevent recurrent neurological events (8,15–18). However, both surgical closure and long-term anticoagulation therapy have significant associated morbidity. An alternative option is transcatheter device closure of the foramen ovale (19–26). Preliminary reports using the Bard Clamshell Septal Occluder Device (Bard Clamshell Septal Umbrella, USCI Division, C. R. Bard, Billerica, Massachusetts) and the Buttoned Device (Pediatric Cardiology and Custom Medical Devices, Amarillo, Texas) to close PFOs for presumed paradoxical emboli have been encouraging (19,20,24,25). Recently, the CardioSEAL Septal Occluder Device (NMT Medical Inc, Boston, Massachusetts), a second-generation version of the Bard Clamshell Septal Occluder Device, has become available for transcatheter device closure.

We have previously reported our initial experience with transcatheter closure of PFO using the Bard Clamshell Septal Occluder Device in patients believed to be at high risk for recurrent neurological events due to paradoxical
emboli (19). This study extends the follow-up for this cohort of patients with additional patients included who had undergone placement of either the CardioSEAL Septal Occluder Device or Buttoned Device for presumed paradoxical emboli.

METHODS

Patient population. Patients were included who underwent transcatheter closure of a PFO at Children’s Hospital in Boston, Massachusetts or Massachusetts General Hospital, Boston, following one or more presumed paradoxical systemic events. All patients had had prior evaluations regarding the etiology of systemic embolic events, including transient ischemic attacks (TIA), cerebrovascular accidents (CVA), peripheral embolic events or brain abscesses in the absence of any other identifiable cause of systemic emboli, and were believed to have had presumed paradoxical emboli. The characteristics and prior evaluations of patients who had undergone placement of the Bard Clamshell Septal Occluder Device have been previously reported (19). Evaluation of individual patients varied but included magnetic resonance imaging (MRI), computed tomographic (CT) examinations, cerebral angiography, carotid ultrasounds, Holter monitoring, echocardiography and lower extremity noninvasive evaluation. All patients had evidence of a PFO by transthoracic or transesophageal echocardiography. A PFO was defined as a valve-like opening between septum primum and septum secundum without evidence of an anatomic defect in the septa. Patients with another known etiology for an embolic event, or other structural heart disease, including secundum atrial septal defects, were excluded.

All patients were enrolled in investigational protocols approved by the Food and Drug Administration as well as by the internal review board for each respective hospital or underwent device placement emergently on a case-by-case basis. Informed consent was obtained in all patients. Patients enrolled at Children’s Hospital underwent transcatheter closure with the Bard Clamshell Septal Occluder Device (Clamshell) between March 1989 and October 1994, and with the CardioSEAL Septal Occluder Device (CardioSEAL) between September 1996 and November 1997. Patients enrolled at Massachusetts General Hospital underwent transcatheter closure with the Buttoned Device between January 1995 and November 1997.

Device implantation. The design and technique of transcatheter device implantation across the interatrial septum for the Clamshell and Buttoned Devices have been described previously (19–22). The technique of implantation of the CardioSEAL Device is similar to that of the Clamshell Device. In order to provide a generally well tolerated form of antithrombotic therapy for a period of time until the device becomes fully endothelialized, which in experimental animal models can occur between four and 12 weeks, daily aspirin therapy was recommended for a period of six months following device placement. A percentage of patients who were receiving anticoagulant therapy with warfarin prior to device placement, continued on warfarin therapy following device placement because of other medical conditions such as hypercoagulable state, multiple deep vein thrombosis (DVT) episodes or malignancy.

Data collection. Data were collected from research and hospital records, as well as through communication with referring physicians. The investigational protocols specified evaluation, including a history, physical examination, chest X-ray, electrocardiogram and transthoracic echocardiography, at one, six and 12 months following device implantation, and subsequently at yearly intervals with data obtained per protocol when possible. Follow-up data were obtained from March 1989 to May 1998. Device position and stability were determined by transthoracic or transesophageal two-dimensional echocardiography. Among the different protocols, the presence and grade of any residual atrial level shunt were determined by transthoracic or transesophageal echocardiography using Doppler color mapping or agitated saline solution contrast injection. The grading of residual leaks for the Clamshell, CardioSEAL and Buttoned Devices were similar and categorized as none to trivial (no detectable leak or <1 mm in the diameter of the color jet), mild (1 to 3 mm in diameter color jet) and moderate (>3 mm in diameter color jet).

Statistical analysis. An actuarial risk of recurrent embolic events at the time of the latest event was determined using the Kaplan-Meier life table analysis method. The annual risk of recurrence was calculated from the actuarial risk using the following formula:

\[ R_{annual} = 1 - \left[1 - R_{actuarial}\right]^{1/\text{years}}. \]

Statistical analysis was performed using software (SAS 6.12; SAS Institute; Cary, North Carolina).

RESULTS

Patient characteristics. A total of 63 patients were enrolled in the study: 28 in the Clamshell group, 13 in the CardioSEAL group and 22 in the Buttoned Device group (Table 1). The mean age was 46 years (range, 20 to 79 years) and the male-to-female ratio was 1.3:1. The reason for referral was CVA in 55 patients, TIA in 5 patients, brain
Residual Shunt Follow-up. The mean follow-up was 2.6 years (Table 2).

7 (11%) patients and moderate shunts remained in 2 (3%) device placement or subsequently. Mild shunts remained in 54 of 63 (86%) patients at the time of occluder. Effective closure (trivial or no residual shunt) was accomplished in 54 of 63 (86%) patients at the time of device placement and residual shunt.

In the Buttoned Device group, and CardioSEAL Device groups, all patients had successful deployment and residual shunt. Effective use (6%).

Device placement and residual shunt. In the Clamshell and CardioSEAL Device groups, all patients had successful deployment of the device. In the Buttoned Device group, two patients required deployment of a second counter-occluder due to suboptimal positioning of the first counter-occluder. Effective closure (trivial or no residual shunt) was accomplished in 54 of 63 (86%) patients at the time of device placement or subsequently. Mild shunts remained in 7 (11%) patients and moderate shunts remained in 2 (3%) (Table 2).

Follow-up. The mean follow-up was 2.6 ± 2.4 years (0.1 to 8.2 years) for a total of 164 patient-years (Table 3). There were four deaths during the follow-up period, none of which was believed to be related to the device: one death was from sepsis following a hip fracture in a patient with end-stage renal failure, a second was from a pulmonary embolism in a patient who had a hypercoagulable state and prior to device placement had had multiple pulmonary embolisms and CVAs, a third death was from lung cancer and a fourth death was from leukemia.

At the time of the procedure, 39 (62%) patients were using anticoagulation therapy whereas at the time of follow-up, 11 (17%) of the patients were using anticoagulation therapy with 29 (46%) receiving aspirin (Table 3).

No patients had documented atrial fibrillation or flutter prior to implantation of the device. Four patients were noted to have atrial fibrillation during or subsequent to device placement; two had transient atrial fibrillation during device implantation and two had paroxysmal atrial fibrillation noted during the follow-up period. Of the latter two, one occurred at two weeks and the second at three months following device closure. Both of these patients at the time of last follow-up were noted to be in sinus rhythm.

Recurrent neurological events. There were four recurrent neurological events: one stroke and three transient events. The recurrent stroke occurred in a 56-year-old woman who had suffered two CVAs before device placement and had undergone an extensive neurological evaluation, including magnetic resonance angiography and carotid ultrasonography that showed no stenoses, normal results from a Holter monitor and normal protein C, S and antithrombin III levels. An echocardiogram had demonstrated a hypermobile interatrial septum with a PFO and evidence of significant right-to-left shunt flow on agitated saline solution contrast injection. Because the etiology of her multiple CVAs was believed to be due to paradoxical emboli, she underwent closure of her foramen with a CardioSEAL Device. New neurological symptoms subsequently developed in this patient six months following device placement, and another brain MRI scan showed evidence of a new stroke. A transesophageal echocardiogram showed a well seated device without evidence of residual shunting by color Doppler or agitated saline solution contrast injection. The interatrial septum was no longer hypermobile.

There were three transient neurological events without evidence of permanent neurological residua. One occurred in a 31-year-old woman with a history of a stroke, who had right-sided visual disturbances three months following placement of a Clamshell Device. A CT scan of the head showed no evidence of a new stroke, and a transesophageal echocardiogram revealed a well seated device with evidence of a mild residual shunt. Because of a persistent residual shunt, she was offered another attempt at complete closure with another device or surgical closure. She elected to undergo surgical closure. At the time of surgery, the surgeon decided not to remove the device, as it had become fully endothelialized, and sutured closed a small residual defect.

A second event occurred in a 44-year-old man who...
developed a transient episode of blurred vision and slurred speech three years following placement of a Clamshell Device. A CT scan of his head showed no evidence of a cerebral infarction. Echocardiography demonstrated a left atrial mass that appeared to be associated with a fractured left atrial device arm that was approximating the posterior wall of the left atrium (“friction lesion”). The device was well seated and there was no evidence of residual shunt flow. This patient underwent surgical removal of the device and mass and closure of his foramen without complications.

The third event occurred in a 19-year-old male patient who had a brain tumor and who had multiple transient neurological symptoms that his neurologists believed were atypical for this patient's brain lesion. Evaluation had demonstrated a PFO that was closed with a Clamshell Device prior to the patient initiating chemotherapy. Following device closure, this patient continued to have similar neurological symptoms.

Risk of recurrent neurological event. A Kaplan-Meier lifetable analysis for the 63 patients in this study revealed an actuarial risk of recurrent neurological events of 9.5% at 3.1 years (95% confidence interval, 0%, 20.3%) resulting in a calculated annualized risk of 3.2% (Fig. 1). Stratification of this analysis by potential predictors of recurrent events following device closure, including age, gender, presence of residual shunt, warfarin anticoagulation following device, device type and multiple neurological events prior to device, revealed no significant differences (Table 4).

Complications. Device arm fractures have been described previously for both the Clamshell and CardioSEAL Devices (19,27–30). Ten of 28 patients in the Clamshell Device group were noted to have fractures, one of which, as previously stated, was associated with a friction lesion from rubbing of the fractured device against the left atrial wall. There have been no significant complications associated with the remaining nine patients with fractures. In the CardioSEAL Device group, 5 of 13 patients were noted to have incidental device arm fractures at routine follow-up visits. There have been no complications associated with these device arm fractures, and none of these patients have had surgical removal of their devices.

Two of 22 patients in the Buttoned Device group underwent surgical closure of PFO because of malalignment of the device with significant residual shunting. Both

Table 3. Follow-up Data

<table>
<thead>
<tr>
<th>Device</th>
<th>n</th>
<th>Follow-up (yr)</th>
<th>Deaths</th>
<th>Recurrent Neurological Events</th>
<th>Surgical Repair</th>
<th>Warfarin Therapy After Device</th>
<th>ASA Therapy After Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clamshell</td>
<td>28</td>
<td>4.7 ± 2.2</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>CardioSEAL</td>
<td>13</td>
<td>0.6 ± 0.3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Buttoned</td>
<td>22</td>
<td>1.3 ± 1.0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
<td>2.6 ± 2.4</td>
<td>4 (6%)</td>
<td>4 (6%)</td>
<td>4 (6%)</td>
<td>11 (17%)</td>
<td>29 (46%)</td>
</tr>
</tbody>
</table>

ASA = aspirin.

Figure 1. Kaplan-Meier analysis of the recurrence rate of stroke or transient ischemic attack following transcatheter device closure.

Table 4. Stratified Kaplan-Meier Lifetable Analyses

<table>
<thead>
<tr>
<th></th>
<th>Annualized Event Rate (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤45</td>
<td>6.4</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;45</td>
<td>7.9</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3.6</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>18.1</td>
<td></td>
</tr>
<tr>
<td>Residual shunt</td>
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<td></td>
</tr>
<tr>
<td>Trivial or none</td>
<td>3.3</td>
<td>NS</td>
</tr>
<tr>
<td>Mild or moderate</td>
<td>37.6</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.0</td>
<td>NS</td>
</tr>
<tr>
<td>No</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Device type</td>
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<td></td>
</tr>
<tr>
<td>Clamshell</td>
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<td>NS</td>
</tr>
<tr>
<td>CardioSEAL</td>
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<td></td>
</tr>
<tr>
<td>Buttoned</td>
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<td></td>
</tr>
<tr>
<td>Multiple prior events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9.5</td>
<td>NS</td>
</tr>
<tr>
<td>No</td>
<td>12.6</td>
<td></td>
</tr>
</tbody>
</table>

NS = not significant.
patients had successful initial device placement and were noted on the six-month follow-up echocardiography to have partial malalignment of the devices with significant residual shunting. Both underwent successful surgical removal of the devices and closure of their PFOs.

**DISCUSSION**

The present study reports the intermediate follow-up of patients following transcatheter closure of PFO for presumed paradoxical emboli at two institutions with particular reference to the incidence of recurrent embolic neurological events. Among 63 patients followed up for a mean of 2.6 years (164 patient-years), there were four recurrent neurological events: one stroke and three transient events. Actuarial analysis of these data revealed an annualized risk of 3.2% for recurrent stroke or TIA following transcatheter closure of the foramen.

**Estimation of recurrence risk in patients with stroke and PFO.** A number of studies have estimated the recurrence risk of stroke or TIA following an initial stroke in patients with PFO (1,31–34). In one of the larger series examining this, Bogousslavsky et al. (1) followed up 140 patients (mean age, 44 years) with an initial stroke or TIA and a PFO, noting a risk of recurrent stroke or TIA of 3.8% per year (14); however, depending on the presence of certain risk factors, they predicted recurrence rates to be >50% in high risk groups. In another study by Mas et al. (34), in which 132 patients with cryptogenic stroke and PFO (mean age, 40 years) were examined for recurrent stroke or TIA following an initial neurological event, the calculated recurrence risk ranged from 3.4% to 11% per year.

Although the above-mentioned studies provide insights into the risk of recurrent stroke or TIA in patients with stroke and a PFO, direct comparison of prior studies to this present study should be made with caution, as the patient populations differ in important ways. Most notably, 43% of patients in the present study had multiple neurological events prior to entry into the study, suggesting that they may have been at higher risk for a recurrent event compared with the patients in previously published studies, all of whom had had only one neurological event at the time of entry.

The wide range of recurrence rates noted in prior studies underscores the difficulties in identifying patients at greatest risk of recurrent neurological embolic events attributable to a PFO. Although paradoxical embolism has been recognized increasingly as a cause of embolic stroke, it is often a diagnosis of exclusion, as direct demonstration of the passage of emboli through the foramen is rare (1,7,19,35). Consequently, there are inevitably patients in whom presumed embolic events are erroneously attributed to paradoxical emboli. For example, in the present study, one patient had a recurrent stroke following device placement despite a normally positioned device and without evidence of a residual shunt by color Doppler or agitated saline solution contrast injection during transesophageal echocardiography, suggesting that the etiology of her multiple prior strokes was, in fact, not due to paradoxical emboli. A similar experience was reported by Homma et al. (8) who noted four recurrent neurological events among 28 patients despite successful surgical closure of the PFO. The success of any technique designed to prevent recurrent paradoxical embolic phenomena will depend highly on the success with which patients at high risk for true paradoxical emboli can be identified.

In addition, the success of device closure in particular will also depend on closure of the PFO with full endothelialization. In two of our patients, technical factors with suboptimal device performance may have contributed to recurrent events. As the experience with these devices increases, however, there are likely to be modifications that may reduce the incidence of such problems.

**Study limitations.** Because of the small number of recurrent events, this study was underpowered to detect clinically important differences when stratifying by age, gender, residual shunt, anticoagulation during follow-up, device type and history of multiple neurological events prior to device closure. In addition, this study was without a true control group, lacking even a comparable historical comparison, preventing one from drawing a clear conclusion regarding the impact of transcatheter closure on the risk of recurrent neurological events. Such a relationship would be best demonstrated through a randomized clinical trial. Nevertheless, transcatheter closure of the PFO appears to be a promising option, especially in patients who are unable to tolerate long-term anticoagulation or who are poor surgical candidates in the treatment of paradoxical embolism.

**CONCLUSIONS**

Transcatheter closure of PFO is an alternative therapy in the prevention of presumed paradoxical emboli in selected patients. Improved device performance may reduce the risk of recurrent neurological events. Further studies are necessary to identify the patients most likely to benefit from this intervention, particularly relative to alternative therapies such as surgical closure of the PFO or long-term anticoagulation.

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**REFERENCES**


3. Webster MWI, Chancellor AM, Smith HJ, Swift DL, Sharpe DN,


