Transcatheter Closure of Interatrial Communications for Secondary Prevention of Paradoxical Embolism

Single-Center Experience

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Background—Patients with a patent foramen ovale (PFO) after cerebral, coronary, or systemic embolic events of presumed paradoxical origin are at risk for recurrent thromboembolism. We report our single-center experience of interventional closure of interatrial communications for secondary prevention of presumed paradoxical embolism.

Methods and Results—Since 1997, percutaneous closure of interatrial communications was performed at our institution in 66 patients (mean age 47.8±12.7 years; 31 males) with a PFO or an atrial septal defect and at least 1 documented presumed paradoxical thromboembolic event. Fifty-eight patients had cerebral embolism, 10 had coronary embolism, and 3 had peripheral embolism. Several patients experienced multilocal arterial embolism. Fifty-four patients had a PFO, 33 of them with an atrial septal aneurysm, and 12 had an atrial septal defect. The implantation procedure was successful and without complication in all patients. After 3 months, only 2 patients showed a residual shunt, which disappeared in both cases after 12 months. In 112.2 patient-years of follow-up (range, 5 weeks to 3.5 years), we have not seen any recurrent thromboembolic event.

Conclusions—Interventional closure of interatrial communications is a safe and effective therapeutic option for the secondary prevention of presumed paradoxical embolism. To further evaluate this strategy, randomized trials comparing interventional closure with anticoagulation have been initiated by us and others. (Circulation. 2002;105:2845-2848.)

Key Words: cerebral ischemia ■ embolism ■ heart septal defects ■ stroke

In the last 10 years, patent foramen ovale (PFO) and atrial septum aneurysm (ASA) were identified as potential sources of cerebral and systemic embolism. In younger patients (≤55 years) with cryptogenic strokes, Lechat et al1 demonstrated a higher prevalence of PFO (54%) compared with a control group (10%). Other authors confirmed these results in the following years.2–4 The risk of recurrent cerebrovascular events was further elevated if the PFO was associated with an ASA.5,6 Stone et al7 showed an increased risk for subsequent ischemic neurological events despite antiplatelet or anticoagulant therapy if interatrial right-to-left shunting was considerable as demonstrated by transesophageal contrast echocardiography. Paradoxical embolism other than cerebral is rarely reported, and only a few case reports exist about coronary embolism.8

For prevention of a paradoxical embolic event, antiaggregatory or anticoagulant agents and transcatheter or surgical closure of the PFO are the principal therapeutic options. However, no comparative studies are available. In a study by Stone et al,7 31% of patients with large shunts through a PFO had recurrent ischemic neurological events during a mean follow-up time of 21 months despite antiplatelet or anticoagulant therapy, thus establishing the need for alternative therapies. Therefore, many efforts have been undertaken to develop implantable devices that can be used for interventional closure of PFOs and atrial septal defects (ASDs).9–12

However, in a recent study by Windecker et al13 using 5 different types of closure devices, the periprocedural complication rate was 10% in 78 patients, including embolization of device parts, periprocedural transient ischemic attack (TIA), or stroke caused by air embolism, cardiac tamponade, and retroperitoneal hematoma. Initial results with the Amplatzer occluder in children14–16 and adults17 with ASD and PFO18 were promising in terms of efficacy and safety.

Methods

Patient Population

Between November 1997 and August 2001, percutaneous closure of interatrial communications was performed at our institution in 66 patients with a PFO or ASD (mean age 47.8±12.7 years, range, 16 to 71 years) and at least 1 documented presumed paradoxical thromboembolic event. The patients were suitable for inclusion in the study if the following criteria were met: (1) clinical and/or radiological (CT, MRI, or angiography) evidence of a thromboembolic event, into either the brain, the heart, or a peripheral artery; (2)
presence of a spontaneous or provokable right-to-left shunt through an interatrial communication (a PFO with or without ASA or an ASD) confirmed by transesophageal contrast echocardiography; and (3) thorough exclusion of any cause for the vascular event other than the interatrial communication, ie, atherosclerosis of the extracranial cerebral arteries, coronary atherosclerosis in case of a coronary embolic event, chronic or intermittent atrial fibrillation, left heart thrombus, or significant mitral valve abnormalities. Evidence of a venous thrombosis was not a prerequisite for inclusion. All patients gave written informed consent before the implantation procedure.

Transesophageal Echocardiography
For preinterventional diagnosis, peri-interventional guidance, and postinterventional follow-up, an HP SONOS 5500 echocardiography system (Hewlett-Packard) with a multiplane transesophageal probe was used. The transthoracic studies were performed with 4- or 8-MHz transducers and second harmonic imaging. The contrast agent used was Echovist (Schering AG Berlin).

In addition to standard transthoracic imaging, transesophageal echocardiography (TEE) was performed to visualize the interatrial septum and to exclude thrombi, especially in the left atrial appendix, or other structural abnormalities. The criteria of an ASA diagnosed by TEE included a diameter at the base ≥15 mm and an excision of septum secundum with an amplitude ≥15 mm. A PFO was defined as the appearance of microbubbles across the interatrial septum (with or without Valsalva maneuver) and the absence of a color Doppler jet indicating left-to-right shunt. If in addition to the right-to-left shunt during contrast injection, a left-to-right shunt was seen in the color Doppler, the defect was defined as an ASD. Interventional closure of the interatrial communication was offered to the patient if a PFO or ASD with or without ASA was confirmed by TEE and no other cause for systemic thromboembolism was found.

Implantation Technique
The interatrial communication was passed under fluoroscopic guidance with a 6F multipurpose catheter. In all patients, stretch size of the PFO or ASD was determined with an NMT (NMT Medical Corp) or an AGA (AGA Medical Corporation) sizing balloon. After the diagnostic procedure was completed, a 9F long sheath was placed through the atrial septum. At this time, the TEE probe was inserted. The chosen device was mounted on the delivery system and loaded into the transseptal sheath, with care taken to prevent air embolism. Then, the occluder was advanced through the sheath into the left atrium until the left atrial part of the device was unfolded. After that, the whole unit was withdrawn under fluoroscopic and echocardiographic control against the interatrial septum. After it was determined that the device was in the correct position, the introducer sheath was further withdrawn while constant tension was applied on the delivery cable until the right atrial part of the device unfolded. If the position of the device was stable, it was unscrewed.

All patients received antibiotic prophylaxis (Flucloxacillin 2 g IV) during the procedure, as well as 6 and 12 hours later. Discharge from the hospital was scheduled for the next day.

Results

Postinterventional Treatment
All patients received aspirin 100 mg/d for 6 months. For the same period, they were advised to take standard antibiotic endocarditis prophylaxis during procedures with a known risk of bacteremia.

Follow-Up Examinations
Follow-up visits that included Holter ECG and transthoracic echocardiography were scheduled at discharge and after 4 weeks, 3 months, 6 months, and 1 year. Thereafter, patients were followed up by telephone calls or by contact with their referring physicians. After 3 months, TEE with intravenous contrast injection was performed to detect any residual shunt at rest and after a Valsalva maneuver.

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**TABLE 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Type of Device</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFO</td>
<td>54</td>
<td>81.8</td>
</tr>
<tr>
<td>with ASA</td>
<td>33</td>
<td>61.1</td>
</tr>
<tr>
<td>ASD</td>
<td>12</td>
<td>18.2</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31</td>
<td>47.0</td>
</tr>
<tr>
<td>Female</td>
<td>35</td>
<td>53.0</td>
</tr>
<tr>
<td>Number of events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>41</td>
<td>63.2</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>27.9</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>8.8</td>
</tr>
</tbody>
</table>

**Type of event**
- Cerebrovascular embolism 53 80.3
- Coronary embolism 5 7.6
- Cerebrovascular and coronary embolism 5 7.6
- Peripheral embolism 3 4.5
- Cardiovascular risk factors
  - Arterial hypertension 22 33.3
  - Hyperlipoproteinemia 36 54.5
  - Smoking 17 25.8
  - Diabetes mellitus 2 3.0
- Thrombophilia 4 6.0

**TABLE 2. Closure Devices**

<table>
<thead>
<tr>
<th>Type of Device</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplatzer PFO Occluder (APO)*</td>
<td>40</td>
<td>60.6</td>
</tr>
<tr>
<td>25/35 mm</td>
<td>37/3</td>
<td></td>
</tr>
<tr>
<td>Amplatzer Septal Occluder (ASO)*</td>
<td>22</td>
<td>33.3</td>
</tr>
<tr>
<td>PFO-Star†</td>
<td>2</td>
<td>3.0</td>
</tr>
<tr>
<td>Cardioseal‡</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Starflex‡</td>
<td>1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Manufacturers: *AGA Medical Corporation, Golden Valley, Minn; †Applied Biometrics Inc, Burnsville, Minn; ‡NMT Medical Inc, Boston, Mass.
Follow-Up

Recurrence Paradoxical Embolism

During a follow-up of 112.2 patient-years (range, 5 weeks to 43 months), no recurrent paradoxical embolic events were observed. This compares with 95 events in 93 observed patient-years (beginning with the first documented event in every patient; range, 1 week to 15 years) before closure of the interatrial defect.

Residual Right-to-Left Shunt

In 2 patients, 3 months after the procedure (1 PFO Star, 1 ASO device), a small left-to-right shunt was seen in the TEE examination; after 6 and 12 months, these shunts were no longer detectable.

Arrhythmias

In 2 patients, brief asymptomatic episodes of atrial fibrillation were observed by Holter ECG monitoring. These patients were advised to take coumadin to achieve an international normalized ratio of 2.0 to 2.5.

Discussion

In several studies, a strong association between the presence of a PFO with or without ASA and cryptogenic stroke in younger patients (<55 years) has been shown. Paradoxical thromboembolism through the PFO is a presumed cause of these events, which often lead to permanent disability. However, even in patients with atrial septal abnormalities, other potential causes of cerebral and coronary arterial occlusion have to be evaluated. These include direct embolization from the ASA, formation of a thrombus as a result of atrial arrhythmia, and unelucidated mechanisms. Therefore, we used the term "presumed paradoxical embolism" for patients in whom all known causes of arterial thrombosis and thromboembolism had been thoroughly excluded. We excluded patients with atrial arrhythmias in the preinterventional Holter monitoring from the interventional treatment, and we excluded patients with atherosclerosis.

After a first paradoxical embolic event, the risk for recurrence is 3.4% to 3.8% per year. The French PFO and ASA Study Group has recently shown that the recurrence risk is higher if the PFO is associated with an ASA (15.2% in 4 years) than in patients with a PFO alone (2.3%). In patients with an ASA without PFO, their group has not seen any recurrence, but the number of patients in this subgroup of their study (n=10) is too low to exclude an ASA alone as a possible cause of systemic thromboembolism. In the present study, in the majority of patients (33 of 54), the PFO was associated with an ASA. Patients with an ASA alone (without provokable right-to-left shunting) were not considered for interventional therapy. Alternatives for secondary prevention of recurrent thromboembolic events include oral anticoagulation, the effectiveness of which is ill defined and which places the patient at considerable risk of bleeding complications, or surgical closure of the defect, which offers no proven benefit in prevention of further events.

Homma et al reported 28 patients followed up after surgical closure of the defect and found a recurrence rate of stroke or TIA of 19.5% within 13 months. Ruchat et al found no recurrences after surgical closure over 1.5 years in 32 patients aged <60 years. In contrast, in the study by Dearani et al in 91 patients, the risk for recurrence of a TIA was 7.5% within the first year and 16.6% within 4 years. The considerable differences between these studies may be related to different surgical techniques or different criteria for patient selection and follow-up.

Recently, percutaneous interventional closure techniques became available. The early experiences of Bridges et al with the Clamshell device in 28 patients resulted in 4 recurrent TIAs during the follow-up period of 1 to 24 months. Implantation of the buttoned device by Ende et al in 10 patients with ASD or PFO was complicated by embolization of the counter-occluder into the left atrium in 1 patient. In the remaining 9 patients, no recurrent paradoxical embolic event was observed during a mean follow-up of 32 months. In a multicenter trial using the ASDOS device for closure of ASD and PFO, recurrent TIA occurred in only 1 of 46 patients with PFO, but that trial had a high rate of periprocedural and postprocedural complications (1% embolization, 3% pericardial effusion, 6% thrombus formation on the device, and 2% infection).

Windecker et al reported 80 patients treated with 5 different occluder types. A recurrence for the combined end point of TIA, stroke, and peripheral embolism was found in 3.4% per year. Similarly, Hung et al reported a recurrence rate of 3.2% per year, most of which was associated with residual shunts, as in the series by Windecker et al. This recurrence rate is in the same range as that in the Lausanne study. In that series of 340 patients, treatment consisted of aspirin (66%), oral anticoagulation (26%), or surgical closure (8%).

However, given a higher procedural success rate (complete closure in all patients after 12 months and in 64 of 66 after 3 months), as reported in the present study, the recurrence rate may be much lower. We did not observe any recurrent paradoxical embolic event or recurrent neurological deficit in more than 112 patient-years of follow-up. Our number of residual shunts (3% at 3 months) compares favorably to the 27% reported by Windecker et al and the 14% reported by Hung et al. The annual risk for recurrence of paradoxical embolism was 6.8% in patients with versus 2.1% in patients without a residual right-to-left shunt (relative risk 4.2) in the report by Windecker et al, which underscores the importance of complete closure of the defect.

In 1 of our 2 patients with a residual shunt, who was treated with an 8-mm Amplatzer septal occluder to close a PFO, the shunt disappeared after 12 months. The PFO of the other patient had been closed by a 26-mm PFO Star device, and no right-to-left shunt was seen after 6 months. We did not observe any residual shunting in patients in whom the defects were closed with the recently developed Amplatzer PFO occluder (n=40). This device is characterized by an umbrella that is larger on the right atrial side (25 or 35 mm) than on the left side.

In the present study, a relatively high number of patients had presumed paradoxical coronary embolism (10 of 66 patients). We based this diagnosis on the finding of a myocardial infarction (confirmed by symptoms, typical ECG
changes, enzyme elevations, and hypokinesis or akinesis in the left ventricular angiogram) in patients without coronary atherosclerosis demonstrated by coronary angiography, without any other embolic causes such as valvular heart disease or atrial arrhythmia, thus using the same criteria as for presumed cerebral embolism. In addition, we excluded focal coronary spasm in response to acetylcholine in all patients investigated except those with acute myocardial infarction. The high percentage of myocardial infarction in patients with a PFO has not been addressed in the literature appropriately before and might have been overlooked because most of the patients with infarctions had an uncomplicated course and only moderate enzyme elevation. Whereas Crump et al recently could not find a higher incidence of PFO in patients with acute myocardial infarction and angiographically normal coronary arteries, their series was largely underpowered to answer this question given the background of the high event rates of acute myocardial infarction in Western countries and the multiplicity of potentially underlying pathophysiological causes (eg, other arterial embolisms, spasms, and coronary plaques undetected by angiography). Moreover, only trans-thoracic contrast echocardiography was performed, without the use of second harmonic imaging. TEE is superior in detecting ASA, a condition that is known to be associated with a higher risk for paradoxical embolism and which we found in 33 of 54 patients with PFO in our cohort and in 5 of 10 patients with presumed paradoxical coronary embolism.

In conclusion, our results show that the interventional closure of interatrial communications is a safe and effective therapeutic option for the secondary prevention of presumed paradoxical embolism. To further evaluate this strategy, randomized trials comparing interventional closure with anticoagulation have been initiated by us and others.

References

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