Percutaneous PFO closure with Amplatzer PFO occluder: predictors of residual shunts at 6 months follow-up

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Abstract

OBJECTIVE: The objective of this study was to assess predictors of residual shunts after percutaneous patent foramen ovale (PFO) closure with Amplatzer PFO occluder (AGA Medical Corporation, Golden Valley, MN, USA). METHODS: All percutaneous PFO closures, using Amplatzer PFO occluder performed at a tertiary center between May 2002 and August 2006, were reviewed. Follow-up, including saline contrast transesophageal echocardiography, was performed in all patients 6 months after the intervention. PATIENTS: A total of 135 procedures were performed. Mean age of the patients was 51 years. The indication for PFO closure was an ischemic cerebrovascular event in 92%, paradoxical systemic embolism in 4%, and a diving accident in 4%. Recurrent events prior to PFO closure were noted in 34%. A concomitant atrial septal aneurysm was present in 61%. RESULTS: At 6 months follow-up, a residual shunt was detected in 26 patients (19%). Residual shunts were more common in patients with an atrial septal aneurysm (27 vs. 8%, P= .01) and in patients treated with a 35-mm compared with a 25-mm device (39 vs. 15%, P=.01). A concomitant atrial septal aneurysm remained independently associated with residual shunts when controlled for body mass index, gender, age, atrial dimensions, and presence of a Chiari network (odds ratio 4.1, 95% confidence intervals 1.1-15.0). CONCLUSION: The presence of atrial septal aneurysms in patients undergoing percutaneous PFO closure with an Amplatzer PFO occluder significantly increases the rate of residual shunts at 6 months follow-up, even if 35-mm devices are used.
Percutaneous PFO closure with Amplatzer PFO occluder:
Predictors of residual shunts at six months follow up.

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Abstract

Objectives: To assess predictors of residual shunts after percutaneous PFO-closure with Amplatzer PFO occluder.

Methods: All percutaneous PFO closures, using Amplatzer PFO occluder performed at a tertiary centre between May 2002 and August 2006 were reviewed. Follow-up, including saline contrast transesophageal echocardiography was performed in all patients six months after the intervention.

Patients: A total of 135 procedures were performed. Mean age of the patients was 51 years. The indication for PFO closure was an ischemic cerebrovascular event in 92%, paradoxical systemic embolism in 4% and a diving accident in 4%. Recurrent events prior to PFO closure were noted in 34%. A concomitant atrial septal aneurysm was present in 61%.

Results: At 6 months follow-up a residual shunt was detected in 26 patients (19%). Residual shunts were more common in patients with an atrial septal aneurysm (27% versus 8%, p = 0.01) and in patients treated with a 35mm compared to a 25mm device (39% versus 15%, p = 0.01). A concomitant atrial septal aneurysm remained independently associated with residual shunts when controlled for body mass index, gender, age, atrial dimensions and presence of a Chiari network (odds ratio 4.1, 95% confidence intervals 1.1-15.0).

Conclusion: The presence of atrial septal aneurysms in patients undergoing percutaneous PFO closure with an Amplatzer PFO occluder significantly increases the rate of residual shunts at six months follow-up, even if 35mm devices are used.
Introduction

In patients with stroke of unknown etiology (cryptogenic stroke) and a patent foramen ovale (PFO), percutaneous closure has been advocated as an alternative strategy to lifelong antithrombotic therapy, particularly in the presence of associated atrial septal aneurysms and in young individuals. While several types of occluders for PFO device closure are available in the market, the Amplatzer PFO occluder (AGA Medical Corporation, Golden Valley, Minnesota) currently is still the most widely used. One limitation of any percutaneous device closure is the possible persistence of a residual shunt, which may occur in up to 29% [1]. An association between residual shunts and recurrent ischemic events has been demonstrated [2,3,4,5] but little is known about predictors of residual shunts after percutaneous PFO-closure.

Aim of the study

We sought to identify predictors of a residual shunt six months after percutaneous PFO closure with the Amplatzer PFO occluder.

Methods

Patient population: All patients, referred for interventional closure of a PFO at a single tertiary centre between May 2002 and August 2006, were included. All patients were assessed by a standardized protocol including transthoracic (TTE) and transesophageal echocardiography (TEE) before device closure and 6 months thereafter. The echocardiographic studies included the injection of agitated saline contrast into an antecubital vein to demonstrate a right to left shunt, either at rest or following the Valsalva manoeuvre. It was
considered positive if bubble contrast in the left atrium was noted within the first 3 cardiac cycles after their appearance in the right atrium. An atrial septal aneurysm was defined as a maximum deflection of the atrial septum of at least 15mm on M-Mode recording perpetual to the atrial septum [6]. The devices used were 25mm- and 35mm-Amplatzer PFO occluders at the discretion of the operator. The procedure was performed under local anaesthesia and fluoroscopic control, without periprocedural echocardiography. All patients were loaded with Aspirin prior to the procedure and oral double antiplatelet therapy with Aspirin and Clopidogrel was maintained for 3 months, followed by Aspirin only for an additional 3 months. Patients with a history of previous stroke or TIA were kept on treatment with low dose Aspirin thereafter, irrespective of the presence of a residual shunt. A chest radiograph was performed routinely the day after the procedure. All patients had an outpatient follow up visit after six months, including a comprehensive transthoracic and transesophageal echocardiography with saline contrast injection.

**Outcomes:** The main outcome measure was the presence of a residual interatrial shunt at six months follow-up, detected by TTE or TEE after intravenous injection of agitated saline contrast. Secondary outcome measures were recurrence of ischemic events, periprocedural complications and complications during follow-up.

**Statistical analysis:** Continuous variables were expressed as means (±SD), and differences among the groups of patients were tested with Student’s t-test. Categorical data were presented as actual numbers and percentages, and a Chi-squared test was used to test for differences among the groups.
Patient and procedural characteristics (indication for PFO closure, presence of an atrial septal aneurysm, size of the device used, gender, age at implantation, presence of a Chiari network in the right atrium, atrial size and body mass index) were tested as predictors for residual shunts. When a significant predictor for a residual shunt was identified in the univariate analysis it was further evaluated by means of a multiple logistic regression. Statistical significance was assumed with a two-sided p value < 0.05.

Results

Patients and procedures: A total of 135 consecutive procedures were performed. The mean age of the patients was 51 (+/- 12) years with a range of 21 to 75 years. Fifty-eight percent of patients were male and 36% were older than 55 years. Demographic and baseline characteristics are summarized in table 1.
Table 1: Baseline characteristics, atrial septal anatomy and indication for PFO closure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>patients (n = 135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (+/- SD) (years)</td>
<td>51 (+/- 12)</td>
</tr>
<tr>
<td>Age &gt; 55 years (%)</td>
<td>48 (36)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>78 (58)</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>History of dyslipidemia (%)</td>
<td>53 (39)</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>37 (27)</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>30 (22)</td>
</tr>
<tr>
<td>Positive family history (%)</td>
<td>24 (18)</td>
</tr>
<tr>
<td>Body mass index (+/- SD) (kg/m²)</td>
<td>25.4 (+/- 4)</td>
</tr>
<tr>
<td>Isolated PFO (%)</td>
<td>53 (39)</td>
</tr>
<tr>
<td>Concomitant atrial septal aneurysm (%)</td>
<td>82 (61)</td>
</tr>
<tr>
<td>Reason for PFO closure</td>
<td></td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>93 (69)</td>
</tr>
<tr>
<td>Transient ischemic attack (%)</td>
<td>31 (23)</td>
</tr>
<tr>
<td>Stroke or TIA (%)</td>
<td>124 (92)</td>
</tr>
<tr>
<td>Paradoxical peripheral embolism (%)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Diving accident (%)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Recurrent embolic events (%)</td>
<td>46 (34)</td>
</tr>
</tbody>
</table>

The index event for closure of the PFO was a transient ischemic attack in 23%, an ischemic stroke in 69%, paradoxical peripheral embolism in 4% and a diving accident in 4% of patients. Thirty four percent of patients had recurrent ischemic events prior to the intervention. Thirty-nine percent of patients had an isolated PFO, whereas in 61% of patients a concomitant atrial septal aneurysm was present. There was no difference between patients with and without recurrent embolic events regarding the presence of an atrial septal aneurysm (57% and 63% respectively, p-value = 0.58).

To choose the most appropriate device size, transthoracic and transesophageal echocardiograms were carefully reviewed before every procedure. None of the patients included in this series had a multifenestrated ASA or multiple defects within the interatrial septum. The decision, whether to
use a 25mm or a 35mm device was based on a qualitative assessment of the size of the ASA and the size of the PFO on preprocedural TEE. No formal sizing procedure was performed. A 35mm Amplatzer PFO occluder was used in a total of 23 cases (17%), 21 of whom had a concomitant atrial septal aneurysm (25.6% of all patients with atrial septal aneurysms). In 19 patients the 35mm device was chosen based on findings on preprocedural TEE and in four patients after the smaller device had either prolapsed or its position had appeared unstable during the procedure itself.

**Outcomes:** Echocardiography at six months follow up detected a residual interatrial shunt in 26 patients (19.3%). In a semiquantitative manner, 10 out of those 26 shunts (38%) were considered to be significant (right to left shunt with more than 20 bubbles counted in the left atrium, either spontaneously or after the Valsalva manoeuvre). The residual shunt was localized at the circumference of the device in 12 patients and across the discs of the device in 6 patients. In eight patients with a persistent right to left shunt on saline contrast echocardiography, the localization of the shunt remained undetermined, including 3 patients, in whom a residual shunt was only detected on transthoracic study after release of the Valsalva manoeuvre. In none of the patients with a residual shunt a separate defect within the interatrial septum was detected on TEE.

Comparing the groups with and without residual shunts there were no differences in baseline characteristics such as gender, symptoms, age, or body mass index. With respect to anatomical variables, no difference was found regarding atrial dimensions and the presence of a Chiari network (see *table 2*).
Table 2: Univariate predictors of residual shunts at 6 months follow-up

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Residual shunt numbers / numbers at risk</th>
<th>%</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated PFO</td>
<td>4 / 53</td>
<td>8</td>
<td>0.01</td>
</tr>
<tr>
<td>PFO/ atrial septal aneurysm</td>
<td>22 / 82</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>25mm PFO-occluder</td>
<td>17 / 112</td>
<td>15</td>
<td>0.01</td>
</tr>
<tr>
<td>35mm PFO-occluder</td>
<td>9 / 23</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Male patients</td>
<td>16 / 78</td>
<td>21</td>
<td>0.84</td>
</tr>
<tr>
<td>Female patients</td>
<td>10 / 57</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Age &gt; 55 years</td>
<td>12 / 48</td>
<td>25</td>
<td>0.3</td>
</tr>
<tr>
<td>Age &lt;55 years</td>
<td>14 / 87</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>BMI &gt; 25</td>
<td>8 / 53</td>
<td>15</td>
<td>0.4</td>
</tr>
<tr>
<td>BMI &lt; 25</td>
<td>18 / 82</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>RA long axis &gt; 50mm</td>
<td>6 / 30</td>
<td>20</td>
<td>0.9</td>
</tr>
<tr>
<td>RA long axis &lt; 50mm</td>
<td>20 / 105</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Chiari network present</td>
<td>7 / 30</td>
<td>23</td>
<td>0.7</td>
</tr>
<tr>
<td>Chiari network not present</td>
<td>19 / 105</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

A residual shunt was significantly more prevalent in patients with a concomitant atrial septal aneurysm, as compared to those patients with an isolated PFO (27% versus 8%, p = 0.01). A residual shunt was also more common in patients treated with a 35mm Amplatzer PFO occluder, compared to those having received a 25mm device (39% versus 15%, p = 0.01). Of all cases in whom a 35mm occluder had been used, only two patients had had an isolated PFO without atrial septal aneurysm. Both patients had a large PFO at baseline and neither of them had a residual shunt at follow-up. When tested in a logistic regression model, including presence of an atrial septal aneurysm, body mass index, gender, age at implantation, atrial dimensions, and presence of a Chiari network, only the presence of an atrial septal aneurysm was significantly associated with a residual shunt at follow-up (odds ratio 4.1, 95% confidence intervals 1.1-15.0). There remained a trend towards more residual shunts (odds ratio 3.2, 95% confidence intervals 0.9-11.6, p = 0.075) even when controlled for the size of the device used.
A subset of 12 patients (46%) with residual shunts underwent repeat transesophageal echocardiography 12 months after implantation. This investigation demonstrated the disappearance of the residual shunts in two out of nine patients (22%) with 35mm occluder and in 1 out of 17 patients with 25mm occluder. Both shunts

One patient with a large residual 6 months after implantation of a 35mm device underwent a second procedure with implantation of a 25mm device, which completely sealed the residual defect.

**Secondary endpoints:** Two patients (1.5%) had recurrent ischemic events during follow up. The first patient had been treated with a 35mm PFO device and a residual shunt was detected at follow up. He suffered a diving accident, without permanent sequelae. The second patient had been treated with a 25mm occluder and had no detectable residual shunt at follow up. He suffered a transient ischemic attack without permanent sequelae.

Periinterventional complications occurred infrequently. There was one device embolization during the procedure in a patient with a large atrial septal aneurysm. The device was removed percutaneously and the PFO was successfully closed with a larger device during the same procedure. Vascular access complications were observed in 2.2% of cases. These included two pseudo-aneurysms, treated with thrombin injection and one arterio-venous fistula, which spontaneously closed a few weeks later. In four patients (3%) transient atrial fibrillation at the time of device implantation was recognized. All those episodes terminated spontaneously after a maximum of 12 hours. At six
months follow-up one patient was incidentally found to have a thrombus on the left atrial disc and in one patient, the ECG showed asymptomatic atrial fibrillation. Both patients were treated with oral anticoagulation and both remained free of embolic complications 12 and 18 months after the intervention.

Discussion

The rate of residual interatrial shunts after PFO closure with Amplatzer devices has been investigated in several studies [1,2,3,5,7,8,9,10,11,12,13,14,15,16,17]. However, direct comparison of the results of these studies is difficult. Although different types of devices have been used in several series, a differentiation of shunt rates for different device types was not always reported. In addition the methods of follow up were not uniform regarding time and modality of follow up. For example, not in all series a TEE with saline contrast was routinely performed in follow up. Comparable larger series with similar follow up modalities, described rates of residual shunts at 6 months follow up of 8-19%. [2,3,5,10,14,17]. In our patient group, we found a high rate of 19% residual shunts at 6 months. This might partly be explained by the high percentage of concomitant atrial septal aneurysms in our series, reflecting the restrictive referral policy at our institution. Therefore there may have been a bias towards more residual shunts as mainly patients with large atrial septal aneurysms were referred for PFO closure. Only few series investigated predictors of residual shunts at follow up [3,5,17]. The higher rate of residual shunts in the presence of an atrial septal aneurysm
could be demonstrated only in some series [5,17]. Zajarias et al [17] described a residual shunt at 6 months follow up after percutaneous PFO closure with Amplatzer devices in 7/7 patients in the presence of an atrial septal aneurysm. Wahl et al [5] clearly demonstrated an association of a residual shunt with larger devices. This finding could not be demonstrated in the series of Zajarias [17]. In our series a 35mm occluder was used almost exclusively in patients with atrial septal aneurysms and thus, the size of the device could not be demonstrated to be an independent predictor of residual shunts.

Several factors may play a role for the fact, that residual shunts were more prevalent in patients with an atrial septal aneurysm and especially in those in whom a 35mm occluder was used. First, even the 35mm occluder may be too small to fully cover a large atrial septal aneurysm as is shown in figure 1.
Figure 1: Fluoroscopic views after implantation of an Amplatzer 35mm occluder in a patient with PFO and large atrial septal aneurysm. Panel A depicts the occluder at the time of implantation (large arrow) showing a good hold on the secundum atrial septum (small arrow). Panel B shows the situation 10 months later, after a large residual shunt was detected on echocardiography. The device has slipped off the septum secundum (arrow).

Second, in patients in whom a 35mm occluder is needed, the larger device may unfavourably alter the atrial septal geometry and therefore prevent proper alignment of the occluder to the atrial septum (see figure 2).
Figure 2: Incomplete apposition of an Amplatzer 35 mm PFO occluder (large arrow) to the atrial septum (small arrow) before (panel A) and after (panel B) release of the device. The arrowhead points to the gap between atrial septum and device.

Third the larger surface of the 35mm device might delay endothelialization [14]. The latter hypothesis would be supported by the finding of disappearance of a residual shunt in some patients with large devices after one year follow up.

To overcome the problem of frequent residual shunts in patients with large atrial septal aneurysms the use of other devices, for example Amplatzer ASD occluder, or the use of alternative implantation techniques, for example through a prior transseptal puncture, might be considered. Compared to the Amplatzer PFO occluder with its narrow waist, the Amplatzer ASD occluder is
a self-centering device, which may proof beneficial in patients with a large PFO/ASA.

**Study limitations**

The main limitation of our study is the small size of our patient group and therefore the small number of patients with residual shunts. To what extent the rate of residual shunts decreases after longer follow up has not been investigated routinely. Due to the short follow up period we could not determine, whether these mainly small residual shunts translate into a higher rate of recurrent ischemic events.

**Conclusion**

The presence of atrial septal aneurysms in patients undergoing percutaneous PFO closure with an Amplatzer PFO occluder significantly increases the rate of residual shunts at six months follow-up, even if 35mm devices are used.
References


