Echocardiographic findings in simple and complex patent foramen ovale before and after transcatheter closure

Antonio Vitarelli*, Enrico Mangieri, Lidia Capotosto, Gaetano Tanzilli, Ilaria D’Angeli, Danilo Toni, Alessia Azzano, Serafino Ricci, Attilio Placanica, Ennio Rinaldi, Khaled Mukred, Giuseppe Placanica, and Rasul Ashurov

Sapienza University, Via Lima 35, Rome 00198, Italy

Received 20 May 2014; accepted after revision 29 June 2014; online publish-ahead-of-print 19 August 2014

Aims
Percutaneous closure of patent foramen ovale (PFO) in cryptogenic cerebrovascular events is an alternative to medical therapy. The interpretation of residual shunts after implantation of different devices for PFO with different morphologies is controversial.

Methods and results
Transcatheter PFO closure was performed in 123 patients with a history of ≥1 paradoxical embolism using three different devices: Amplatzer (n = 46), Figulla Occlutech (n = 41), and Atriasept Cardia (n = 36). Fifty-six patients presented with simple PFO and 67 patients had complex morphologies. All patients were studied with contrast enhanced transesophageal echocardiography (TEE) before interventional procedure and thereafter at 1 and 6 months and every 6–12 months in case of incomplete closure. Definite closure was confirmed in at least two consecutive TEE studies. Various PFO morphologies were identified by TEE before device implantation. The device size to PFO diameter ratio was significantly increased in patients with complex PFO compared with those patients with a simple PFO morphology (P 0.05). The difference between the closure rate of S-PFO and C-PFO concerning each device type was significant (Amplatzer P 0.0027, Figulla P 0.0043, and Atriasept P 0.01). The mean follow-up period was 3.4 years (median 2.7 years) with a cerebrovascular re-event rate of 2.4% per year. In three patients, thrombi were detected in the 6-month TEE controls and resolved after medical therapy. In three other patients, the implantation of an adjunctive device was necessary for residual shunt.

Conclusion
In our series of patients, the closure rate was dependent on PFO morphology more than occluder size and type. An adjunctive device was implanted in selected cases.

Keywords
Transesophageal echocardiography ● Patent foramen ovale ● Percutaneous transcatheter closure ● Atrial device ● Intracardiac shunt

Introduction
An intracardiac shunt due to patent foramen ovale (PFO) increases the risk of cerebrovascular events (stroke, transient ischaemic attack, or peripheral emboli) due to paradoxical embolism from the right to the left cardiac chambers. The therapeutic options are medical therapy, surgical closure, or percutaneous transcatheter closure. Although results from three recently published randomized controlled trials failed to show a significant benefit of interventional

PFO closure over medical therapy, a systematic review and meta-analysis of existing randomized controlled trials suggest that in patients with cryptogenic stroke PFO closure may be beneficial in reducing the risk of recurrent vascular events when compared with medical treatment and benefit may be greater in patients with a substantial shunt. The combination of PFO and atrial septum aneurysm (ASA) is reported to be associated with an increased risk of recurrent stroke. The risk of recurrent cerebral ischaemic events on oral anticoagulation and or anti-platelet therapy was...
increased in patients with the combination of PFO and ASA in contrast to PFO alone. Previous publications concerning the interventional closure of PFO in combination with ASA showed an increased risk for thrombus formation as well as for incomplete closure. The residual right-to-left shunt after transcatheter PFO closure with and without ASA was reported to be a significant predictor for stroke or transitory ischaemic attack re-event. However, there is still the question of clinical outcome for different catheter devices and the relevance of residual shunting on the recurrence of ischaemic events during long-term follow-up. It has also shown that variations in atrial septal and PFO morphology are frequently encountered and should be carefully assessed prior to percutaneous closure. Our purpose was to analyse the transesophageal echocardiographic aspects of underlying anatomy of PFO, to assess the echocardiographic results on early, mid-, and long-term follow-up after percutaneous implantation, and compare the influence of atrial septal morphology and occluder characteristics of different devices in regard to the time of definite closure.

**Methods**

**Population**

One hundred and twenty-three consecutive patients with a positive history of recurrent paradoxical embolism were enrolled in a non-randomized, prospective follow-up examination. All patients had a positive history of ≥1 embolic events diagnosed by magnetic resonance imaging for cerebral embolism and angiography or MR-angiography in the case of peripheral embolism. Before transcatheter PFO closure, extensive workup consisting of brain and carotid imaging, echocardiography, 12-lead electrocardiography, and a hypercoagulability panel (including tests for protein C, protein S, antithrombin 3, factor V Leiden, anti-cardiolipin antibodies, and antiphospholipid antibodies) was performed in all patients. When no cause was identified, a stroke was labelled as being cryptogenic in origin. All patients were also evaluated by a neurologist.

Patients with atrial fibrillation and/or the presence of a significant valvar or coronary artery disease with a surgical indication were not considered for interventional closure. Inclusion to follow-up required sinus rhythm at the beginning of the study and the agreement to perform transesophageal echocardiographic and transthoracic echocardiographic studies. Peri-interventional transesophageal echocardiography (TEE) studies were used to analyse atrial septum and fossa ovalis communications and choose the maximum acceptable device size for implantation. Three different devices were used according to device and size availability: (i) Amplatzer PFO occcluder (St Jude Medical, St Paul, MN, USA; diameters 18, 20, 25, and 32 mm), (ii) Figulla Occlutech (Occlutech, Helsingborg, Sweden; diameters 15, 16, 25, and 26 mm), and (iii) Atrisept Cardia (Cardiac Inc., Eagan, MN, USA; diameters 20, 25, and 30 mm).

Forty-eight consecutive patients with PFOs identified incidentally on transesophageal echocardiographic bubble studies, and without any histories of stroke or TIA or any other embolic event were used as a control group.

**Echocardiography**

Two-dimensional echocardiography was performed with commercially available ultrasound scanners (Vivid-I or Vivid-E9, GE Medical Systems, Fairfield, CT, USA), a broadband transthoracic transducer, and a multi-plane transesophageal 5 MHz transducer. For TEE, mild sedation with midazolam and local pharyngeal anaesthesia (lidocaine) were used. Blood pressure, pulse oximetry, and the electrocardiogram were monitored. After insertion of the probe, a comprehensive two-dimensional and colour and spectral Doppler transesophageal echocardiographic examination was performed. Images of fossa ovalis were obtained in midoesophageal view as well as other planes to optimize the view of the septum primum overlapping the septum secundum. Colour Doppler mapping was adjusted to have Nyquist velocities ranging from 28 to 55 cm/s during atrial septal interrogation.

The following TEE morphological characteristics were studied (Figures 1 and 2): (i) PFO size was the maximum separation between the septum primum and septum secundum at the point of exit into the left atrium in multiple views in end-diastolic frames; (ii) Tunnel length was the maximum overlap between the septum primum and septum secundum measured in multiple views; a tunnel was classified as being a long tunnel when the length was ≥8 mm and greater than the dimension of either the PFO entrance (right atrial margin) or exit (left atrial margin); (iii) ASA was defined as a membrane excursion of the interatrial septum of at least 10 mm with a base diameter of the aneurysm of at least 15 mm (patients with a hypermobile septum, which is movement of 5–10 mm in either direction in multiple views, were included to the group of patients with a simple PFO); (iv) Septum primum deviation was defined as a deviation of the overlapping part of the atrial septum primum from the atrial septum secundum, separating a tent-shaped area from the left atrium; this malalignment of the primary atrial septum, with or without a PFO, has also been defined ‘double atrial septum or ‘spiraling septum’.
Figure 2: Transesophageal representative images of complex PFO. (A) PFO associated with atrial septal aneurysm. (B) PFO with long tunnel. (C) PFO with septum primum deviation. (D) PFO with thick septum secundum. (E) PFO with prominent Eustachian valve. (F) PFO associated with small ASD. AN, aneurysm; ASD, atrial septal aneurysm; EV, Eustachian valve; LA, left atrium; RA, right atrium; SP, septum primum; SPD, septum primum deviation; SS, septum secundum; T, tunnel.
from those traversing a PFO or bubbles retrogradely flowing into the shunt from those due to provoked opening of an intermittent PFO as well discern late bubbles entering the left atrium on the basis of intrapulmonary the Valsalva manoeuvre, and normal respiration resumed as the first, defined as Grade 0 if no bubbles could be detected. Grade 1 was attributed echocardiologist (A.V.). Spontaneous or induced right-to-left shunt was to traverse the atrial septum or alternatively to enter the left atrium within abdominal and consequently intrathoracic pressure as well as the right pressing the patient’s abdomen was used in an attempt to increase the oeuvre creating sufficient intrathoracic pressure to decrease preload, and implantation as a means of judging the effectiveness of the Valsalva manœuvre. Since coughing was rarely effective when the patient was too sedated, sufficiently to also increase the right atrial-to-left atrial pressure gradient. A PFO or residual or with additional multiple small defects on the fossa ovalis, or with the other defects of the fossa ovalis.15 Complex PFO was defined as a PFO with a tunnel length of ≥ 8 mm, or with multiple openings into the left atrium, or with atrial septal aneurysm, or with septum primum primum deviation, or with additional multiple small defects on the fossa ovalis, or with the presence of a large bulky Eustachian ridge, or with excessive redundant Chiari network.

Contrast echocardiography
A gelatin-based plasma expander (4.0% gelofusine, B. Braun, Melsungen, Germany) was used as contrast. Together with a small amount of air (5–10% mixture), it was agitated between two syringes mounted on a 3-way stopcock immediately before a bolus injection via a 20-gauge venous cannula introduced into the right antecubital vein. The Valsalva manoeuvre was conducted at each study visit and repeated until opacification of the right atrium and interatrial septum was considered of sufficient quality.21–23 Contrast was injected during the strain phase of the Valsalva manoeuvre, and normal respiration resumed as the first bubbles appeared in the right atrium. Each patient received a large number of contrast injections during high-quality TEE.21 The presence of leftward bulging of the interatrial septum during the three beats that followed opacification of the right atrium was used prior to device implantation as a means of judging the effectiveness of the Valsalva manœuvre creating sufficient intrathoracic pressure to decrease preload, and sufficient to also increase the right atrial-to-left atrial pressure gradient. Since coughing was rarely effective when the patient was too sedated, pressing the patient’s abdomen was used in an attempt to increase the abdominal and consequently intrathoracic pressure as well as the right atrial-to-left atrial gradient during the release phase. A PFO or residual shunt was determined on contrast appearance of micro bubbles visualized to traverse the atrial septum or alternatively to enter the left atrium within three cardiac cycles of opacification of the right atrium. The images were reviewed during the procedure and offline by a single experienced echocardiologist (A.V.). Spontaneous or induced right-to-left shunt was defined as Grade 0 if no bubbles could be detected. Grade 1 was attributed if <10 bubbles were seen. Grade 2 was defined if ≥10 bubbles up to a distinct contrast jet opacification was seen and Grade 3 if a severe filling of >25% of a left heart chamber was recorded.22,23 Care was taken to discern late bubbles entering the left atrium on the basis of intrapulmonary shunt from those provoked by opening of an intermittent PFO as well as to differentiate bubbles shunting from the right upper pulmonic vein from those traversing a PFO or bubbles retrogradely flowing into the pulmonic veins after entering the left atrium through a PFO.24

Device implantation
The interatrial septum was crossed under fluoroscopic and TEE guidance with a 6F multipurpose catheter after documenting normal pressure values in the pulmonary artery and right heart. PFO size and morphology were determined by TEE without balloon sizing. Depending on the device used, a 9–12 French long sheath was placed across the atrial septum. After flushing the loaded implantation system to prevent air embolism, the device was placed under fluoroscopic and TEE guidance and the early success of closure was tested by a venous injection of right heart echo contrast agent. All patients received antibiotic prophylaxis (curoxim 2 g) 1 h prior to the procedure. Discharge from the hospital was on the next day after post-interventional transthoracic echocardiography and 12-lead ECG examination.

Follow-up
All patients were prospectively investigated for at least 6 months up to 4 years. The routine initial follow-up programme included a TTE study at Day 1, a TTE study at 1 month, and a TEE study at 6 months after the intervention. When complete closure of the device was documented for the first time, we requested a second study 6 months later by TEE to confirm definite closure. In case of persistent residual shunt at follow-up, the TEE examination was repeated every 6 months until closure was documented twice. Re-events were defined cerebral ischaemic events as well as peripheral embolism. In regard to cerebral ischaemic events, neurological reports and additional cerebral imaging procedures were obtained. As antithrombotic therapy, all patients received aspirin 100 mg daily and clopidogrel 75 mg daily for 6 months. Then, clopidogrel was discontinued in all patients and aspirin therapy was maintained for further 12 months.

Statistics
Data are presented as mean value ± SD. Linear correlations, univariate, and multivariate analysis were used for comparisons. Student’s t-test was used to compare mean values for continuous variables, and a χ2 analysis was used for categorical variables. Agreement was tested using k statistics. All tests were two tailed, and differences were considered statistically significant when the P-value was <0.05.

Results
The demographic data of all PFO patients are given in Table 1. One hundred and twenty-three patients had cerebrovascular accidents (CVAs) and underwent percutaneous closure and 48 patients had no CVAs. PFO was a simple flap in 86 patients and complex in 85 patients. Complex PFO included an isolated atrial septal aneurysm in 39 patients, a long tunnel type in 45 patients, a septum primum deviation in 8 patients, a small additional ASD in 9 patients, and a prominent Eustachian valve in 14 patients.

Data on implanted patients are given in Table 2. Three patients with PFO closure were lost on follow-up resulting in a complete assessment of 123 patients (98.3%). Three different PFO occlusion devices (46 Amplatzer PFO occluders, 41 Figulla, and 36 Atriasept devices) were used. Cardiovascular risk factors were similar in patients with different devices. Severe shunting predominated in complex PFOs. The degree of shunting worsened with increasing PFO size (Figure 3). PFO diameters were greater in the group with severe shunting compared with the group with mild (P < 0.001) and moderate (P < 0.001) shunting, and in patients with complex morphologies compared with patients with simple PFO (P < 0.05).

The distribution of device sizes employed for PFO closure and the morphologies of PFO are outlined in Figure 4. The diameter of the occluder varied according to the size of the atrial septum and the size of PFO (simple and complex) at the TEE examination prior to implantation. The device size to PFO diameter ratio was significantly increased in patients with an aneurysm of the septum and complex PFO compared with those patients with a simple PFO morphology (mean, 3.7:1 vs. 2.5:1, P < 0.05).
### Table 1  PFO anatomy in patients with and without CVA

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 171)</th>
<th>With CVA events (n = 123)</th>
<th>Without CVA events (n = 48)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 ± 11</td>
<td>54 ± 18</td>
<td>52 ± 14</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>84/87</td>
<td>60/63</td>
<td>22/26</td>
<td>n.s.</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.82 ± 0.13</td>
<td>1.87 ± 0.16</td>
<td>1.85 ± 0.14</td>
<td>n.s.</td>
</tr>
<tr>
<td>Simple PFO, n (%)</td>
<td>86 (50)</td>
<td>56 (46)</td>
<td>30 (63)</td>
<td></td>
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<tr>
<td>Diameter (mm)</td>
<td>3.3 ± 1.4</td>
<td>3.4 ± 1.6</td>
<td>2.7 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>Complex PFO, n (%)</td>
<td>85 (50)</td>
<td>67 (55)</td>
<td>18 (38)</td>
<td></td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td>4.1 ± 1.5</td>
<td>4.3 ± 1.4</td>
<td>3.1 ± 1.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Tunnel length (mm)</td>
<td>11.3 ± 5.6</td>
<td>13.6 ± 5.2</td>
<td>9.1 ± 4.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Associated ASA, n (%)</td>
<td>39 (46)</td>
<td>33 (49)</td>
<td>6 (33)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Small additional ASD, n (%)</td>
<td>9 (11)</td>
<td>8 (11)</td>
<td>1 (6)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Prominent Chiari’s network, n (%)</td>
<td>14 (16)</td>
<td>12 (18)</td>
<td>2 (11)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Tunnel ≥ 8 mm, n (%)</td>
<td>45 (53)</td>
<td>37 (55)</td>
<td>8 (44)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Prominent Eustachian valve, n (%)</td>
<td>18 (11)</td>
<td>19 (12)</td>
<td>4 (11)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Prominent Chiari’s network, n (%)</td>
<td>8 (9)</td>
<td>7 (10)</td>
<td>1 (6)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Associated ASA, n (%)</td>
<td>39 (46)</td>
<td>33 (49)</td>
<td>6 (33)</td>
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<td>&lt;0.01*</td>
</tr>
<tr>
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<td>7 (10)</td>
<td>1 (6)</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

ASA, atrial septal aneurysm; ASD, atrial septal defect; BSA, body surface area; CVA, cerebrovascular accident; PFO, patent foramen ovale.

*a*With vs. without CVA.

*b*Simple vs. complex PFO.

### Table 2  Baseline characteristics of implanted patients

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 123)</th>
<th>Amplatzer (n = 46)</th>
<th>Figulla (n = 41)</th>
<th>Atriasept (n = 36)</th>
<th>Simple PFO (n = 56)</th>
<th>Complex PFO (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54 ± 18</td>
<td>53 ± 13</td>
<td>52 ± 14</td>
<td>51 ± 18</td>
<td>52 ± 12</td>
<td>51 ± 13</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>60/63</td>
<td>22/24</td>
<td>20/21</td>
<td>19/17</td>
<td>27/29</td>
<td>35/32</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.87 ± 0.16</td>
<td>1.84 ± 0.15</td>
<td>1.81 ± 0.13</td>
<td>1.79 ± 0.15</td>
<td>1.83 ± 0.14</td>
<td>1.85 ± 0.12</td>
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<td>Cardiovascular risk factors</td>
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<tr>
<td>Systemic hypertension, n (%)</td>
<td>47 (38.2)</td>
<td>17 (36.9)</td>
<td>15 (36.7)</td>
<td>15 (41.7)</td>
<td>21 (37.5)</td>
<td>26 (38.8)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>7 (5.7)</td>
<td>3 (6.5)</td>
<td>2 (4.9)</td>
<td>2 (5.6)</td>
<td>3 (5.4)</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td>Cigarette smoking, n (%)</td>
<td>34 (27.6)</td>
<td>13 (28.3)</td>
<td>11 (26.8)</td>
<td>10 (27.8)</td>
<td>15 (26.8)</td>
<td>19 (28.3)</td>
</tr>
<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>14 (11.4)</td>
<td>5 (10.9)</td>
<td>5 (12.2)</td>
<td>4 (11.1)</td>
<td>6 (10.7)</td>
<td>8 (11.9)</td>
</tr>
<tr>
<td>Coagulation defects, n (%)</td>
<td>21 (17.1)</td>
<td>8 (17.4)</td>
<td>7 (17.1)</td>
<td>6 (16.7)</td>
<td>11 (19.6)</td>
<td>10 (14.9)</td>
</tr>
<tr>
<td>Degree of shunting</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Mild, n (%)</td>
<td>23 (18.7)</td>
<td>8 (17.4)</td>
<td>8 (19.5)</td>
<td>7 (19.4)</td>
<td>16 (28.6)</td>
<td>7 (13.4)</td>
</tr>
<tr>
<td>Moderate, n (%)</td>
<td>44 (35.8)</td>
<td>16 (34.8)</td>
<td>15 (36.6)</td>
<td>13 (36.1)</td>
<td>19 (33.9)</td>
<td>25 (37.3)</td>
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<tr>
<td>Severe, n (%)</td>
<td>56 (45.9)</td>
<td>21 (45.7)</td>
<td>19 (46.3)</td>
<td>16 (44.4)</td>
<td>21 (37.5)</td>
<td>35 (52.2)</td>
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<tr>
<td>Indication for PFO closure</td>
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<tr>
<td>Ischaemic stroke, n (%)</td>
<td>56 (45.5)</td>
<td>22 (47.8)</td>
<td>18 (43.9)</td>
<td>16 (44.4)</td>
<td>23 (41.1)</td>
<td>33 (49.3)</td>
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<td>Transient ischaemic attack, n (%)</td>
<td>63 (51.2)</td>
<td>22 (47.8)</td>
<td>22 (53.6)</td>
<td>19 (52.8)</td>
<td>31 (55.4)</td>
<td>32 (47.8)</td>
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<tr>
<td>Peripheral embolism, n (%)</td>
<td>2 (1.6)</td>
<td>1 (2.2)</td>
<td>1 (2.4)</td>
<td>0 (0)</td>
<td>1 (1.8)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Diving, n (%)</td>
<td>2 (1.6)</td>
<td>1 (2.4)</td>
<td>0 (0)</td>
<td>1 (2.7)</td>
<td>1 (1.8)</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>

BSA, body surface area.

*P = n.s. simple PFO vs. complex PFO.

*P < 0.05 simple PFO vs. complex PFO.

*Blood pressure > 140/90 mmHg.

*Serum cholesterol level > 200 mg/dL.

*Deficiency of antithrombin III, protein C, protein S; resistance to activated protein C; presence of antiphospholipid antibodies.

*P < 0.01 simple PFO vs. complex PFO.
Results regarding the closure time of simple and complex PFO are presented in Figure 5. Concerning all implanted occluders, in front of a trend towards a difference in closure times between the Amplatzer, Figulla, and Atriasept groups, a significant difference in closure times was observed between complex and simple PFO for each device type (complex vs. simple PFO: Amplatzer \( P = 0.0027 \), Figulla \( P = 0.0043 \), and Atriasept \( P < 0.01 \)). Overall, simple PFO had a success rate of 84.6% at 6 months, 86.2% after 12 months, and 96.7% after 24 months, while complex PFO showed a later closure rate of 79.7, 82.1, and 92.7%, respectively. On average, 102 of 123 patients (83%) had a complete PFO occlusion at 12-month follow-up.

A minimal residual right-to-left shunt persisted in 14 (11%) patients, whereas a moderate or large residual right-to-left shunt was detected in 7 (6%) patients at 12-month follow-up. At multivariate analysis, tunnel length (odds ratio 4.8; 95% confidence interval 1.92–18.48; \( P = 0.003 \)) and ASA extend (odds ratio 3.6; 95% confidence interval 1.76–16.86; \( P = 0.005 \)) were the most predictive independent factors for residual interatrial shunt at 24 months after technically successful percutaneous PFO closure. The mean follow-up period was 3.4 years (median 2.7 years) with a re-event rate of 2.4% per year. Only cerebral vascular re-events were observed. According to the small number of re-events, there was only a trend of higher re-event rate for the Amplatzer vs. the Figulla and Atriasept devices without statistical significance (\( P = 0.067 \)) and for complex PFO vs. simple PFO (\( P = 0.059 \)). Three patients presented further reasons for a cerebral re-event including the presence of atherosclerotic plaques in the aortic arch, pulmonary arteriovenous shunts, and paroxysmal atrial fibrillation. In one patient, an intrapulmonary fistula implied a residual contrast shunting via the left pulmonary veins covert at the initial examination by a large inflow through the PFO and underwent successful transcatheter coil embolization.

Three patients presented with thrombus formation at the device during follow-up that was detected by TEE 6 months after the procedure. All of them were under medication of aspirin 100 mg and clopidogrel 75 mg once daily. One of them had a coagulation defect (resistance to activated protein C) and one patient had abnormal platelet aggregation tests. No thromboembolic complication occurred. The thrombi (4–6 mm in diameter) resolved after therapy with intravenous heparin (activated partial thromboplastin time 1.5–2.0 times normal) and subsequent oral anticoagulation therapy (INR 2.5–3.0) for 3 months.

Among the seven patients who had a moderate or large residual right-to-left shunt at 12-month follow-up, four of them were treated with medical therapy and all had long tunnels that closed 18–24 months later under anti-platelet therapy. In the other three

![Figure 3](https://academic.oup.com/ehjcimaging/article-abstract/15/12/1377/2397633)  
**Figure 3:** Association between PFO size, PFO morphology, and degree of shunting. S, simple PFO; C, complex PFO. The degree of shunting worsened as PFO size increased. *\( P < 0.001 \) (difference in PFO size, mild vs. severe shunt, complex PFO); †\( P < 0.01 \) (difference in PFO size, moderate vs. severe shunt, complex PFO); ‡\( P < 0.05 \) (difference in PFO size, simple vs. complex PFO, severe shunt).

![Figure 4](https://academic.oup.com/ehjcimaging/article-abstract/15/12/1377/2397633)  
**Figure 4:** Bar graphs showing the distribution of device sizes employed for PFO closure and PFO morphologies (S, simple; C, complex). S-PFO is predominant with small devices \( P = 0.04 \), C-PFO predominates with larger devices \( P = 0.03 \).

![Figure 5](https://academic.oup.com/ehjcimaging/article-abstract/15/12/1377/2397633)  
**Figure 5:** Closure rate at 6 and 12 months in simple (S) and complex (C) PFO with different devices (Ampl, Amplatzer; Fig, Figulla; Atr, Atriasept). In complex PFO, closure rate is higher with any device. *\( P = 0.0027 \) C-PFO vs. S-PFO, Amplatzer; †\( P = 0.0043 \) C-PFO vs. S-PFO, Figulla; ‡\( P < 0.01 \) C-PFO vs. S-PFO, Atriasept.
patients, an additional device was implanted because of persistent clinical symptoms (recurrent CVA, persistent migraine, orthodeoxia). One of these patients had a persistently symptomatic long tunnel despite antiaggregant therapy, the second patient had a large perforated atrial septal aneurysm and a second device was placed to close the gap next to the first device at 24 months after the first implantation, and the third patient had a septum primum deviation and received the second device at 18-month follow-up.

**Discussion**

The main findings of the present study were: (i) a number of anatomical atrial variations besides atrial septal aneurysm are involved prior to percutaneous PFO closure; (ii) the occlusion time as determined by residual shunting on contrast TEE is linked more to the morphological features of the atrial septum than the type of the device used; (iii) additional device implantation for residual shunt may be necessary albeit rarely. To our knowledge, this is the first TEE systematic analysis assessing different devices in comparison with complex anatomical variants as determinants of the PFO closure rate.

Our rate of complete closure as determined by the presence of residual right-to-left shunt (83% at 12 months) is in accordance with the data of previous studies, ranging from 80 to 90% at 6- to 12-month follow-up. The analysis of residual shunts should point to the degree of right-to-left shunt as well as the possibility of an extra-cardiac source of shunt. The degree of right-to-left shunt was assessed via contrast TEE in our study as in previous reports. Although transthoracic echocardiography and transcranial Doppler have been advocated for screening for right-to-left shunts because the Valsalva strain may be more forceful, actually the three techniques are complementary. Once the shunt is detected, TEE is more helpful to assess the exact site of the shunt as well as additional anatomic features. Although contrast TEE may result in false-negative injections both before and after PFO closure whenever too little pressure gradient is provided between the left and right atrium, the use of multiple injections increased the sensitivity for detection of PFO. Moreover, the Valsalva manoeuvre can be attempted during TEE, simultaneous with abdominal strain assessment. In case of Valsalva inefficacy, forced abdominal compression and cough can be used to complement the examination. On the other hand, saline contrast studies done without provocative manoeuvres, such as cough or Valsalva manoeuvre, simplify differentiation of late bubbles entering the left atrium on the basis of intrapulmonary shunt from those due to provoked opening of an intermittent PFO. Intrapulmonary shunt was shown to be an independent predictor of ischaemic stroke and transient ischaemic attack and it was indicated as a potentially unrecognized facilitator of cerebral ischaemic events. In one of our patients, an additional intrapulmonary fistula was detected following PFO device implantation and successful transcatheter coil embolization was performed. Future studies assessing the impact of intrapulmonary shunt on recurrence rate in patients after initial ischaemic stroke or TIA would be of great interest.

We also confirm previous reports about the rate of re-events after the percutaneous procedure. In the Lausanne study, the recurrence rate for PFO was 3.8% per year. It has been reported an annual rate of 1.86% following PFO closure vs. 5.42% under standard medical treatment. Other results ranged between 0.7 and 8.5%. In the present study, the re-event rate was 2.4% per year. The small number of re-events precluded to find a correlation between persistent interatrial shunting or the occurrence of thrombi at the occluder and the re-event rate. Further reasons for a cerebral re-event included aortic plaques, pulmonary arteriovenous fistulas, and atrial fibrillation. We adopted the routine procedure of repetitive TEE until closure was confirmed because we believe that TEE has a higher sensitivity and specificity compared with transcranial Doppler and transthoracic echocardiography not only in the detection of residual shunts but particularly in the assessment of additional anatomical atrial variations and thrombus formation. Thrombus was reported in older generation devices, especially in the Starflex group. We had only three patients with thrombus formation, and two of them had coagulation or platelet abnormalities. The changes in device design and the use of anti-platelet drugs cut down the number of thrombus related to device implantation and reduced the incidence of this potential source of embolic re-events to < 2%.

Differently from the results reported by other authors, in our patients, the residual shunt was predominantly related to the complexity of PFO morphology rather than to the potential role of the type of devices. Closure rate at 6 and 12 months with different devices (Amplatzer, Figulla, and Atriasept) was higher with any device in complex PFO compared with simple PFO in front of a trend towards a difference in closure times between the Amplatzer, Figulla, and Atriasept groups. The longest follow-up period was for the Amplatzer devices, due to their earliest availability. The present study included not only patients with ASA but also other anatomical variants. Though the dynamics of paradoxical embolization is related to the interaction of morphological and functional parameters and the size and frequency of venous thrombosis, the combination of PFO and ASA has been described as an increased risk of recurrent embolic events. The presence of an atrial septal defect can alter the intracardiac haemodynamics and favour embolic events, and the presence of a prominent Eustachian valve has been suggested as an alternative factor in considering the patient at risk of paradoxical embolism. Also, a morphological variation even in the defects found within the oval fossa has been reported. In the presence of wide space between the flap valve and the cranial and dorsal margins of the fossa, the defect takes on a spiral aspect that is displayed by two-dimensional or three-dimensional TEE. This spiralling arrangement produces the unusual features described by others as ‘dual atrial septums’ or as malalignment of the primary atrial septum suggested to promote thrombosis in elderly patients. When the margins of the fossa show this unusual configuration, it is preferable to close the defect by choosing an oversized device that covers the full extent of the spiralling margins. One of our patients with septum primum deviation and extensive anterosuperior separation between the flap valve and the rim presented significant residual right-to-left shunt at 6 months after PFO closure and, because of a recurrent TIA, it was decided to implant a second device at 18-month follow-up.

**Clinical implications**

The management of significant residual right-to-left shunt following PFO closure is controversial. The therapeutic possibilities consist of antiaggregant or anticoagulant therapy, transcatheter closure
with an additional device, and surgical treatment. The strength of the present study is the systematic use of TEE and contrast TEE to assess PFO morphology and cardiac and extra-cardiac shunts. In our series of patients, complex PFO variants were more important determinants of the time of complete occlusion than the type of device and thus require more careful monitoring. Closure rate may improve over time, presumably due to device endothelialization, but a second device may be necessary if the residual PFO shunt is associated with clinical events such as recurrent ischaemic stroke/TIA, orthodeoxia, or persistent migraine.

Limitations
First, contrast TEE may result in false-negative injections both before and after PFO closure and Valsalva strain may be highly variable. However, all patients received a considerable number of injections during high-quality TEE and overall the number of contrast injections was remarkable. Secondly, we used three-dimensional TEE only in a few patients but we believe that the systematic use of 3D-TEE would increase the capability to delineate the PFO anatomy. Thirdly, the relatively small number of the patient population and re-events makes the statistical power limited and a larger study would be desirable.

Conclusions
Our results showed that the time of complete occlusion after implantation of a PFO occluder was more dependent on the anatomy of atrial septum than on the type of the device. Although re-events are not associated solely to residual PFO shunt or thrombus formation at the occluder, there is a need for a closer examination of the implanted devices especially in complex variants.

Conflict of interest: None declared.

References


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**IMAGE FOCUS**

Anomalous connection of the left upper pulmonary vein to the vertical vein: an uncommon diagnosis unveiled by suprasternal notch imaging

Armaan Shaikh, Anushree Agarwal, Shannon Treiber, and A. Jamil Tajik*

Aurora Cardiovascular Services, Aurora Sinai/Aurora St. Luke’s Medical Centers, University of Wisconsin School of Medicine and Public Health, 2801 W. Kinnickinnic River Parkway, #840, Milwaukee, WI 53215, USA

* Corresponding author Tel: +1 414 649 3909; Fax: +1 414 649 3551; E-mail: publishing14@aurora.org

A 34-year-old man came to our adult congenital heart disease centre after duplicate superior vena cava (SVC) was incidentally found on chest computed tomography performed for testicular leiomyosarcoma staging. He was asymptomatic. Examination revealed a grade 1/6 ejection murmur at the left upper sternal border. Electrocardiogram and chest X-ray were normal. Transthoracic echocardiography revealed a dilated right atrium (area 19.2 cm²) and a right ventricle (base 4.8 cm and mid 4.5 cm). No atrial septal defect was detected. Suprasternal notch imaging, performed to evaluate the cause of right heart volume overload, revealed a dilated innominate vein (Panel A). Slight leftward tilting of the transducer detected an abnormal red colour Doppler signal, directed towards the transducer to the left of descending aorta (Ao) entering into the innominate vein (Panel B and see Supplementary data online, Video S1). Pulsed-wave Doppler revealed a typical biphasic pulmonary venous flow (Panel C). Anomalous left upper pulmonary venous (LUPV) drainage into the innominate vein via a vertical vein was diagnosed. Contrast-enhanced cardiac magnetic resonance angiography with three-dimensional reformatting (Panel D) showed the anomalous LUPV drainage into the innominate vein via the vertical vein. Other pulmonary veins were normally connected to the left atrium.

This case highlights the key echocardiographic features of anomalous connection of the left pulmonary vein to the vertical vein. It underscores the importance of meticulous imaging via the suprasternal notch window for accurate diagnosis of this rare congenital anomaly with a reported incidence of 0.001 – 0.002%, as transthoracic echocardiography is often the initial diagnostic imaging modality.

LCCA, left common carotid artery; LSA, left subclavian artery; RUPV, RMPV, RLPV, right upper, middle and lower pulmonary veins; IV, innominate vein; VV, vertical vein.

**Conflict of interest:** none declared.

Supplementary data are available at European Heart Journal – Cardiovascular Imaging online.

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