INTRODUCTION

Transcatheter device closure of inter-atrial septal defects, such as atrial septal defect (ASD) and patent foramen ovale (PFO), has become increasingly popular over the past decade. In patients with ASD, a left-to-right shunt results in a chronic volume load of the right heart and pulmonary circulation, which may eventually cause heart failure, arrhythmias and/or pulmonary hypertension. When there are signs of significant volume overload of the right heart (i.e., a dilated right ventricle or a shunt ratio > 1.5:1), the defect is usually closed. Compared to surgery, transcatheter closure of an ASD allows for faster haemodynamic improvement and is associated with fewer complications. Residual shunting after ASD closure may result in persistent volume load of the right heart and pulmonary circulation. In patients with a PFO, right-to-left shunting is associated with cryptogenic stroke, transient ischaemic attack, orthodeoxia, obstructive sleep apnoea, migraine and decompression illness. Although still controversial, several studies have shown that percutaneous PFO closure reduces the risk of stroke and transient ischaemic attack, even when compared to medical therapy. However, treatment success depends on effective closure as residual shunting may be associated with stroke recurrence.
This study aimed at evaluating (1) effective ASD and PFO closure rates, (2) factors related with effective closure, and (3) factors related with events occurring in the follow-up. A total of 32 patients who underwent percutaneous ASD closure with one of four devices [Helex Septal Occluder® (Occultech, GmbH, Jena, Germany), Merit Cardiosoft (VMT Medical Inc., Boston, Massachusetts, USA), or Merit Septal Occluder® (Merit, Arizona, USA)] were followed in our centre from April 2002 and February 2014. All patients who underwent ASD or PFO closure at Jessa Hospital Hasselt between April 2002 and February 2014 were included in the study. Twenty-seven patients (23 with an ASD and 4 with a PFO) were followed in our centre from April 2002 and February 2014. All patients who underwent ASD or PFO closure at Jessa Hospital Hasselt between 2002 and 2014.

METHODS

Patient selection

All patients who underwent ASD or PFO closure at Jessa Hospital Hasselt between April 2002 and February 2014 were included in the study. Twenty-seven patients (23 with an ASD and 4 with a PFO) were followed in our centre from April 2002 and February 2014.

Data collection

Records of all patients were reviewed. Demographic, clinical, echocardiographic and endovascular data were obtained from one records, echocardiography procedures and reports of the interventional procedure. The indications for ASD or PFO closure were reviewed. For patients who underwent ASD closure, the presence of unexplained right ventricular (RV) function and/or RV dilatation was noted semi-quantitatively. For patients who underwent PFO closure, the presence of an aneurysmatic interatrial septum (defined as excursion of the interatrial septum > 20 mm in the left-to-right direction) on transoesophageal echocardiography, was recorded. All patients were invited for follow-up echocardiography procedures. All these two patients had two separate contrast echocardiography studies with an interval of at least 6 months. These two patients were excluded from the effective closure rate analysis. The contrast echocardiography study consisted of injection of agitated geloplasma in an upper extremity vein and bubbles were evaluated in the left atrium within 4 cardiac cycle after opacification of the right atrium and after Valsalva manoeuvre. Mild shunt was defined as the absence of any residual shunt at the last follow-up visit. Valsalva manoeuvres were repeated in each patient. For patients who underwent ASD closure, a presence of a left-to-right shunt was evaluated using colour Doppler echocardiography. The severity of shunt was assessed qualitatively and graded mild or moderate. Adverse events were defined as a composite of all-cause mortality, hospitalisation for heart failure, stroke, TIA and atrial fibrillation and events occurring in the follow-up, using ECG at each follow-up visit or using 24-h recording when indicated.

Statistical analysis

Descriptive statistics continuous variables were reported as mean ± standard deviation. Categorical data were compared using Pearson’s chi-squared test or a chi-square test when appropriate. Cox-regression analysis was performed to evaluate the relationship between baseline variables and effective closure (defined as the absence of any residual shunt at the last follow-up echocardiography). Cox-regression analysis was performed with the following: (1) presence of an ASD, (2) PFO size, (3) presence of right atrial dilatation, (4) presence of right ventricular dysfunction, (5) pulmonary hypertension, (6) presence of an aneurysmatic interatrial septum, (7) previous thrombo-embolic events, (8) right ventricular systolic pressures, (9) pulmonary arterial pressure (PAP), (10) pulmonary vascular resistances, (11) presence of pulmonary hypertension, (12) presence of right heart failure, and (13) presence of right heart decompression illness. Cox-regression analysis was performed using SPSS (version 22.0) for Windows.
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Baseline characteristics

Patient characteristics are summarized in table 1. The implantation procedure was successful in all patients. Pericardiocentesis following ASD closure was necessary in 3% of patients due to left ventricular overload. A total of 4 different devices for ASD patients and 3 different devices for PFO patients were implanted. In ASD patients, mean RV-RA gradient was 36 ± 14 mmHg with 85% of patients presenting with a dilated right ventricle. In PFO patients, aneurysmatic interatrial septum was present in 64% of patients (table 2).

Effective closure rate

In patients who underwent ASD closure, effective closure rate was 72% at 2 years and 93% at 6 years. If only moderate residual shunt was considered, closure rate was 94% at 2 years and 97% at 6 years. If only moderate residual shunt was considered, closure was 94% at 2 years and 97% at 6 years.

Results

Baseline characteristics

Patient characteristics are summarized in table 1. The implantation procedure was successful in all patients. Pericardiocentesis following ASD closure was necessary in 3% of patients due to left ventricular overload. A total of 4 different devices for ASD patients and 3 different devices for PFO patients were implanted. In ASD patients, mean RV-RA gradient was 36 ± 14 mmHg with 85% of patients presenting with a dilated right ventricle. In PFO patients, aneurysmatic interatrial septum was present in 64% of patients (table 2).

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rate was 77% at 2 years and 81% at 6 years. If only moderate shunt is considered, the closure rate was 81% at 2 years and 90% at 6 years (Figure 1). Patients with an aneurysmatic interatrial septum before PFO closure were less likely to be closed when compared to patients without aneurysmatic interatrial septum (HR 0.57; 95% CI 0.33-0.96; \(P = 0.031\)) (table 3 – Figure 2).

### Outcome

During a mean follow-up time of 28 months (range 1-101 months), 9 patients (33%) who underwent ASD closure presented with adverse events. Six patients (22%) developed atrial arrhythmias, 1 (4%) had a stroke and 2 (7%) were hospitalized for heart failure (table 4).

In univariate Cox-regression analysis, age at closure (HR 1.08; 95% CI 1.02-1.16; \(P = 0.016\)), RV-RA gradient (HR 1.09; 95% CI 1.01-1.17; \(P = 0.017\)) and a history of atrial arrhythmias (HR 4.28; 95% CI 1.41-13.7; \(P = 0.007\)) were associated with a higher residual shunt rate.

### Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>1.08</td>
<td>(0.64-1.82)</td>
<td>0.781</td>
</tr>
<tr>
<td>Age at closure</td>
<td>1.01</td>
<td>(0.99-1.03)</td>
<td>0.720</td>
</tr>
<tr>
<td>BMI</td>
<td>0.96</td>
<td>(0.91-1.03)</td>
<td>0.251</td>
</tr>
<tr>
<td>Presence of aneurysmatic IAS</td>
<td>0.57</td>
<td>(0.33-0.96)</td>
<td>0.031</td>
</tr>
<tr>
<td>Device size</td>
<td>0.98</td>
<td>(0.92-1.04)</td>
<td>0.514</td>
</tr>
</tbody>
</table>

BMI: body mass index.

### Table 4

<table>
<thead>
<tr>
<th>Event</th>
<th>ASD N = 27</th>
<th>PFO N = 75</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any residual shunt n (%)</td>
<td>5 (18.5)</td>
<td>15 (20.0)</td>
<td>0.868</td>
</tr>
<tr>
<td>Moderate residual shunt n (%)</td>
<td>4 (14.8)</td>
<td>6 (8.0)</td>
<td>0.329</td>
</tr>
<tr>
<td>Atrial arrhythmia n (%)</td>
<td>6 (22.1)</td>
<td>4 (5.3)</td>
<td>0.011</td>
</tr>
<tr>
<td>Stroke n (%)</td>
<td>1 (3.7)</td>
<td>3 (4.0)</td>
<td>0.946</td>
</tr>
<tr>
<td>Heart failure n (%)</td>
<td>2 (7.4)</td>
<td>0 (0.0)</td>
<td>–</td>
</tr>
<tr>
<td>Death n (%)</td>
<td>0 (0)</td>
<td>2 (2.7)</td>
<td>–</td>
</tr>
</tbody>
</table>

Fig. 1: Effective closure rate in patients undergoing (A) ASD and (B) PFO closure. The blue line indicates closure rate including any residual shunt observed during follow-up echocardiographic contrast studies. The green line indicates closure rate only including patients who had a moderate shunt during follow-up echocardiographic contrast studies.
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CI 1.06-17.40; P = 0.046) were related with adverse outcome (table 5, figure 3). RV-RA gradient before ASD closure was related with age at repair (R² = 0.472; P < 0.0001) (figure 4). RV-RA gradient > 45 mmHg before ASD closure predicted adverse events with a sensitivity of 63% and specificity of 92% (Area under the curve 0.763; P = 0.044) (figure 3).

During a mean follow-up time of 36 months (range 1-105 months), 9 patients (12%) who underwent PFO closure presented with adverse events. Four patients (5%) developed atrial arrhythmias, 2 (3%) had a TIA (both had a clinically and neuroradiologically confirmed transient ischaemic attack) and 2 patients (3%) died (unrelated to cardiovascular disease). In univariate Cox-regression analysis, age at closure was related with adverse outcome (HR 1.09; 95% CI 1.02-1.16; P = 0.012) (table 5). Age at closure > 55 years was related with lower event-free survival (area under the curve 0.795; P = 0.003). Sensitivity and specificity were 70% (figure 6).

Table 5

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95%CI)</th>
<th>P-value</th>
<th>HR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>0.39 (0.08-1.89)</td>
<td>0.239</td>
<td>0.98 (0.24-3.96)</td>
<td>0.977</td>
</tr>
<tr>
<td>Age at closure (y)</td>
<td>1.08 (1.02-1.16)</td>
<td>0.016</td>
<td>1.09 (1.02-1.16)</td>
<td>0.012</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.07 (0.96-1.19)</td>
<td>0.247</td>
<td>1.04 (0.88-1.23)</td>
<td>0.619</td>
</tr>
<tr>
<td>sPAP (mmHg)</td>
<td>1.09 (1.01-1.17)</td>
<td>0.017</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Aneurysmatic septum</td>
<td>– –</td>
<td>0.64 (0.13-3.08)</td>
<td>0.573</td>
<td></td>
</tr>
<tr>
<td>Residual shunt</td>
<td>2.33 (0.44-14.42)</td>
<td>0.336</td>
<td>0.62 (0.08-5.09)</td>
<td>0.659</td>
</tr>
<tr>
<td>History of atrial arrhythmia</td>
<td>4.28 (1.06-17.40)</td>
<td>0.046</td>
<td>– –</td>
<td>– –</td>
</tr>
</tbody>
</table>

BMI: body mass index; sPAP systolic pulmonary artery pressure.
Closure of atrial septal defect type secundum

Closure of atrial septal defect type secundum.

**DISCUSSION**

This study indicated that, although technical success rate was high for percutaneous interventions of the atrial septum, effective closure rate was not 100%. Anatomical characteristics of the atrial septum in patients undergoing percutaneous closure were noted, such as the presence of an aneurysmatic interatrial septum, which was related with lower closure rate. Older age at repair, higher pulmonary arterial pressures, and a history of atrial arrhythmias were related with adverse outcome in those undergoing ASD closure. Older age at repair was related with adverse outcomes in patients undergoing PFO closure. The event rate was significantly higher in patients in whom the PFO was closed using a Helex Septal Occluder® and effective closure rate was significantly higher in patients in whom older devices were used.

**Table 6**

<table>
<thead>
<tr>
<th>Occluder</th>
<th>Number</th>
<th>Age ≥ 55</th>
<th>Neur</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helex Septal Occluder®</td>
<td>4/9</td>
<td>1/15</td>
<td>1/9</td>
<td>0.419</td>
</tr>
<tr>
<td>AMPLATZER Septal Occluder®</td>
<td>2/9</td>
<td>2/31</td>
<td>2/14</td>
<td>0.047</td>
</tr>
<tr>
<td>Occlutech Septal Occluder®</td>
<td>0/14</td>
<td>0/14</td>
<td>1/4</td>
<td>0.131</td>
</tr>
</tbody>
</table>

**Fig. 6** Kaplan-Meier indicating higher effective closure rate in patients who underwent PFO closure using group 1 devices (AMPLATZER PFO occluder and Occlutech PFO occluder) compared to group 2 devices (Helex septal occluder, Cardia PFO occluder and Starflex/Cardioseal occluder).

**Fig. 7** Kaplan-Meier indicating higher effective closure rate in patients who underwent PFO closure using group 1 devices (AMPLATZER PFO occluder and Occlutech PFO occluder) compared to group 2 devices (Helex septal occluder, Cardia PFO occluder and Starflex/Cardioseal occluder).

**Differences between devices**

In 49 patients who underwent PFO closure using a Helex Septal Occluder®, an adverse event was recorded, which was significantly higher when compared to other devices (P = 0.049) (Table 6). When comparing earlier devices (group 1: implanted between 2002 and 2007: Helex PFO Occluder®, Starflex/Cardioseal® and Cardia PFO Occluder®) and more recent devices (group 2: implanted between 2007 and 2013: Amplatzer PFO Occluder® and Occlutech PFO Occluder®), effective closure rate was significantly higher in group 2 (P = 0.027) (Figure 7).
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A closure rate has been reported between 90% to 98% at 1 year after PFO closure, depending on the technique used. Direct medical imaging, the device itself (anatomically shaped devices such as the Amplatzer Septal Occluder, Starfish, and CardioSEAL compared with the younger patients), and anatomical characteristics of the interatrial septum (aneurysmal interatrial septum related to a lower effective closure rate) are important factors. In older patients, a higher effective closure rate can be achieved with the Amplatzer Septal Occluder, Starfish, or CardioSEAL devices compared with the younger patients. A more effective closure rate might have been achieved if follow-up was conducted as scheduled. However, this did not affect all patients equally. Earlier follow-up was performed in PFO patients if there was uncertainty regarding the size of the device. It is assumed that obligatory follow-up in all patients could have resulted in a higher effective closure rate.

CONCLUSIONS

Although technical success is high, the transcatheter ASD and PFO effective closure rate was not 100%. The presence of an aneurysmatic interatrial septum is associated with residual shunting after PFO closure. Pulmonary hypertension in ASD patients and older age at closure in PFO patients are associated with adverse outcomes. Adverse outcome is more frequent with the Helex Septal Occluder. Effective closure rate depends on the device used.

LIMITATIONS

First, this is a single-centre prospective clinical trial with a limited number of patients. However, the number of patients was sufficient to perform association statistics. Second, some of the patients did not undergo follow-up as scheduled and were excluded later to have a consistent dataset. Third, balloon sizing was performed in PFO patients if there was uncertainty regarding the size of the device. It is assumed that obligatory follow-up in all patients could have resulted in a higher effective closure rate. Fourth, the effective closure rate was evaluated using a transthoracic echocardiographic study. With regard to the detection of residual shunts and avoiding false-positives due to transpulmonary shunting, transoesophageal echocardiography may have been more sensitive. For patient comfort, we considered transthoracic echocardiography to be sufficient. Fifth, as ‘older’ devices were used earlier in the learning curve of the operator, this may have added to the lower closure rate observed in these patients.

ACKNOWLEDGEMENTS

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CONFLICTS OF INTEREST

no conflicts to declare.

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