Atrial septostomy in the treatment of severe pulmonary arterial hypertension

F Reichenberger, J Pepke-Zaba, K McNeil, J Parameshwar, L M Shapiro

Background: Atrial septostomy (AS) may improve symptoms and haemodynamics in patients with severe pulmonary arterial hypertension (PAH).

Methods: Twenty AS performed in 17 patients with severe progressive PAH (13 primary pulmonary hypertension, two collagen vascular disease, one thromboembolic disease, one vaso-occlusive disease) were analysed. Seven patients were in NYHA class III and 10 in NYHA IV. Fifteen patients were on long term prostanoid treatment. AS was performed under fluoroscopy using graded balloon technique.

Results: AS improved clinical symptoms and increased the cardiac index from 1.8 to 2.2 l/min/m² and systemic oxygen transport from 263.2 to 329.6 ml/min/m² (p<0.001). Procedure related complications included one non-fatal atrial puncture and one unsuccessful septal puncture. Four patients died within 1 week of surgery from uncontrolled tachyarrhythmia (n=1), severe hypoxaemia (n=1), and multigorgan failure (n=2). One further patient died after voluntarily discontinuing renal dialysis. Twelve patients are alive 5–17 months after the operation with five patients undergoing heart-lung transplantation. There were no differences in haemodynamic and functional parameters between the non-survivors and the mid term survivors. However, the non-survivors were significantly older (52 v 36 years, p<0.01) and had a significantly lower creatinine clearance rate (70 ml/min v 48 ml/min, p<0.05).

Conclusion: Atrial septostomy improves clinical symptoms, cardiac index, and systemic oxygen transport and has the potential to influence the prognosis in selected cases of severe PAH.

Pulmonary arterial hypertension (PAH) is a progressive disease leading to right heart failure (RHF) and often to sudden cardiac death. Without treatment the median survival is 2.8 years, but patients in New York Heart Association (NYHA) class IV have a median survival of only 6 months from diagnosis. Treatment consists of anticoagulation and pulmonary vasodilator therapy with agents such as calcium channel blockers, prostanoids, and bosentan. The only available curative treatment, however, is (heart-)lung transplantation, although this is not an option for every patient. Furthermore, patients continue to deteriorate while on the transplant waiting list due to disease progression.

Atrial septostomy (AS) is a procedure performed in children with a variety of congenital cardiac defects to create an intracardiac shunt. In severe PAH this procedure creates a right-to-left shunt, with decompression of the right ventricle, improvement in haemodynamic parameters, and augmentation of systemic blood flow in both human and animal studies. The created right-to-left shunt improves right ventricular haemodynamics, particularly during exercise, and therefore preserves right ventricular function. Reports in patients with Eisenmenger's syndrome (an anatomical right-to-left shunt) have found better survival in patients with the same degree of pulmonary hypertension than in those with primary pulmonary hypertension.

The initial report of AS in PAH in 1983 was followed by several series showing that AS improves haemodynamics but may be associated with a high post-procedure mortality rate of up to 30%. However, experience with AS in severe PAH is still limited, and the optimal time to perform AS in these severely ill patients (if at all) remains to be established. This report describes our experience of performing AS for severe PAH in a single centre.

METHOD

Patients

Between March 1999 and September 2001, 20 AS were performed in 17 patients (five men) of mean age 40 years (range 18–58). The underlying diagnoses are shown in table 1. Three patients (nos 2, 12, and 14) underwent a repeated procedure due to spontaneous closure of the created septal defect. In patient 14 puncture of the atrial septum could not be achieved at the second AS and this procedure was not included in the haemodynamic calculations but was included in the analysis of outcome.

At the time of AS seven patients were in NYHA class III and 10 in class IV. Twelve patients were treated with continuous intravenous prostacyclin infusion (mean (SD) 13.8 (6.2) ng/kg/min), one with intravenous iloprost (9.9 ng/kg/min), one with subcutaneous UT 15 (25 ng/kg/min), and one with nebivolium iloprost (120 µg total daily dose). Two patients were treated with anticoagulation and diuretics only, one for pulmonary vaso-occlusive disease and the other refused prostanoid treatment.

The indication for AS was the deterioration in clinical and functional status within the previous 3 months. All patients suffered from progressive dyspnoea and additional symptoms as outlined in table 1. Creatinine clearance was calculated according to the Cockcroft formula.

Procedure

A 7 French Swan-Ganz catheter (Edwards Life Sciences, USA) was placed via the right internal jugular vein for haemodynamic assessment including right atrial pressure (RAP), mean pulmonary artery pressure (mPAP), and cardiac index (CI) using the thermodilution method. Measurements were performed immediately before, during, and after AS. Blood samples were drawn for measuring the mixed venous oxygen saturation (Svo₂). AS was performed by one operator (LMS) using a graded balloon dilatation technique. An 8 French

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sheath (Cordis Prefect, Brentford, UK) was passed into the left atrium by Brockenbrough needle puncture (Intervention Ltd, USA). This was introduced across the atrial septum by a modified trans-septal technique using a more posterior position with the needle introduced from below.

A balloon catheter (Cordis Opta LP, Brentford, UK) 8–12 mm in diameter and 40 mm in length was passed across the septum through the sheath on a 1.3 mm guide wire (Intervention Ltd, USA). The sheath was withdrawn to the septum through the sheath on a 1.3 mm guide wire (Intervention Ltd, USA). The sheath was withdrawn to the right atrium and the balloon inflated at low pressure (up to 4 meters) or until the waist was abolished under fluoroscopic control. Serial measurements were made of arterial oxygen saturation (SaO₂), SvO₂, PAP, and cardiac output (CO). To obtain the measurements the balloon was withdrawn into the sheath. To sample in the left atrium the sheath could be readily passed through the atrial septum. The procedure was repeated with increasing balloon sizes until a septal defect could be readily passed through the atrial septum. The procedure could be readily passed through the atrial septum.

Data analysis
Data were normally distributed; the results are displayed as mean (SD). Paired t tests were used to compare differences before and after AS using a level of significance of p<0.05. The Mann-Whitney U test and χ² test were used for intergroup comparisons because of the difference in group size.

### RESULTS

#### Haemodynamic parameters

Mean (SD) right atrial pressure before AS was 12.2 (6.2) mm Hg. Comparison of haemodynamic parameters before and after AS showed an increase in CI of 31% (p<0.001, fig 1). Systemic oxygen transport (SOT) increased by 25% (p<0.001), SaO₂ decreased by 6% (p<0.001), and mPAP decreased by 7% (p=0.26). SvO₂ remained stable (before AS 53.2 (6.9)%, after AS 53.3 (5.8)%). The haemodynamic parameters are outlined in table 2.

The CI calculated by the indirect Fick method was 2.1 (0.4) ml/min/m² before AS and 2.7 (0.6) ml/min/m² after AS, which was significantly higher than CI based on the thermodilution method (p<0.005). When the results of the thermodilution and indirect Fick methods were compared, there was a high correlation between both measurements before and after AS (r=0.83 and 0.78, respectively).

#### Clinical outcome and post-procedure complications

After AS all patients received supplemental oxygen to maintain oxygen saturation at >90%.

The 30 day post-procedure mortality was 25%, with five patients dying during the week after the procedure. One

### Table 1  Patient characteristics and outcome after atrial septostomy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Symptoms</th>
<th>Cr CI (ml/min)</th>
<th>NYHA</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>18</td>
<td>PPH</td>
<td>Diuretics</td>
<td>B, D</td>
<td>86.4</td>
<td>III</td>
<td>Alive after 6 months</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>20</td>
<td>PPH</td>
<td>iv PGI</td>
<td>A, B</td>
<td>81.6</td>
<td>IV</td>
<td>Redo after 6 months, alive 12 months after redo</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>28</td>
<td>PPH</td>
<td>iv PGI</td>
<td>A, B, C, D</td>
<td>69.1</td>
<td>IV</td>
<td>Alive after 8 months</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>35</td>
<td>PPH</td>
<td>iv PGI</td>
<td>B, C</td>
<td>75.2</td>
<td>III</td>
<td>HLTx after 46 days, died 16 months after HLTx (OB)</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>38</td>
<td>VOD</td>
<td>Diuretics</td>
<td>B, D, S</td>
<td>55.6</td>
<td>III</td>
<td>HLTx after 73 days, alive 16 months after HLTx</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>38</td>
<td>PPH</td>
<td>iv PGI</td>
<td>A, B, C, D</td>
<td>91.3</td>
<td>IV</td>
<td>HLTx after 48 days, alive 30 months after HLTx</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>39</td>
<td>PPH</td>
<td></td>
<td>A, B, C, CT</td>
<td>58.2</td>
<td>III</td>
<td>Alive after 5 months</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>40</td>
<td>PPH</td>
<td>iv PGI</td>
<td>B, S</td>
<td>61.8</td>
<td>III</td>
<td>Alive after 17 months</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>40</td>
<td>SLE</td>
<td>iv PGI</td>
<td>B, D, CT</td>
<td>61.8</td>
<td>III</td>
<td>Died after 5 days due to withdrawal from renal dialysis</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>40</td>
<td>PPH</td>
<td>iv PGI</td>
<td>B, D</td>
<td>63.1</td>
<td>III</td>
<td>Died after 5 days due to progressive hypoxaemia</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>42</td>
<td>PPH</td>
<td>iv PGI</td>
<td>A, B, C, CT</td>
<td>83.6</td>
<td>IV</td>
<td>HLTx after 4 months, alive 25 months after HLTx</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>43</td>
<td>PPH</td>
<td></td>
<td>A, B, C, CT</td>
<td>67.7</td>
<td>IV</td>
<td>Redo after 7 months, HLTx 8 months later, alive 11 months after HLTx</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>50</td>
<td>PPH</td>
<td>iv PGI</td>
<td>A, B, CT</td>
<td>45.6</td>
<td>IV</td>
<td>Stroke after 7 months, alive after 17 months</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>53</td>
<td>PPH</td>
<td>iv PGI</td>
<td>A, B</td>
<td>28.1</td>
<td>IV</td>
<td>First AS with ventricular puncture, redo after 3 months failed, died after 1 day in progressive RHF</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>56</td>
<td>PPH</td>
<td>neb Ilo</td>
<td>B, A, D</td>
<td>76.4</td>
<td>IV</td>
<td>Refractory cardiac arrhythmia 6 hours after AS</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>58</td>
<td>TEPH</td>
<td>iv PGI</td>
<td>B, S</td>
<td>43.4</td>
<td>III</td>
<td>Progressive multiorgan failure, died after 1 day</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>52</td>
<td>SSO</td>
<td>iv Ilo</td>
<td>A, B, S</td>
<td>39.5</td>
<td>IV</td>
<td>Alive after 5 months</td>
</tr>
</tbody>
</table>

### Table 2  Haemodynamic parameters before and immediately after AS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before AS</th>
<th>After AS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPAP (mm Hg)</td>
<td>54.8 (10.7)</td>
<td>51.1 (10.6)</td>
<td>0.26</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>93.2 (4.3)</td>
<td>87.4 (5.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>1.7 (0.5)</td>
<td>2.2 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SOT (l/min/m²)</td>
<td>263.2 (66.7)</td>
<td>329.6 (79.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean (SD). mPAP=mean pulmonary artery pressure; SaO₂=arterial oxygen saturation; CI=cardiac index; SOT=systemic oxygen transport.

Figure 1 Mean cardiac index (CI) before and after the procedure in 19 patients who underwent atrial septostomies (excluding the redo in patient 14). A significant increase occurred in mean CI from 1.7 l/min/m² to 2.2 l/min/m² (p<0.001).

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patient (no 15) developed treatment resistant tachyarrhythmia 6 hours after AS. Two patients (nos 14 and 16) died in progressive renal and cardiac failure within 24 hours of the procedure. Patient 14 underwent a repeat AS due to spontaneous closure as previously described. One patient (no 9) was on chronic ambulatory haemodialysis for lupus nephritis. AS improved the haemodynamics and enabled further haemodialysis, but her symptoms recurred and she voluntarily withdrew from renal dialysis. One patient (no 10) developed progressive hypoxaemia after the procedure. Her haemoglobin concentration was at the upper limit of normal. SOT increased by 51% after AS but she died 5 days after the procedure. Necropsy examination showed an atrial septal defect of 8 mm, equalling the size of the dilating balloon. There were no signs of laceration, other cardiac injuries, pericardial effusion, or pulmonary venous congestion.

AS related complications included one atrial puncture with pericardial haemorrhage in patient no 14 which was successfully aspirated (table 1).

There were no significant differences in the haemodynamic and functional parameters between the four patients who died after the procedure (except the patient who stopped renal dialysis) and the 12 mid term survivors. However, those who died had a significantly lower creatinine clearance rate, a higher mean age, and there was a higher proportion of male patients (table 3).

**Follow up**

Two patients (nos 2 and 12) also underwent a repeat AS due to early closure with recurrence of symptoms after 6 and 7 months, respectively. Patient 2 initially improved but, following closure of the second AS, she was further treated with oral sildenafil. Patient 12 successfully underwent heart-lung transplantation (HLTx) 8 months after the second AS. Patient 13 suffered from a minor stroke 7 months after AS, probably due to paradoxical embolism via the created defect despite treatment with intravenous prostacyclin. The patient recovered without neurological deficit and was additionally treated with oral anticoagulation.

Five patients successfully underwent HLTx 46 days to 15 months after AS. Patient 4 died 17 months after HLTx from obliterator bronchiolitis. The remaining seven patients are alive with a follow up of 5–17 months.

**DISCUSSION**

In this study AS improved clinical performance and haemodynamic parameters in patients with severe PAH who were deteriorating on treatment with anticoagulation and prostanoids. AS had an impact on survival, enabling successful bridging to heart-lung transplantation in five patients, and seven patients are still alive 5–17 months after the procedure.

In our study non-fatal complications of AS were rare and included one atrial perforation with pericardial haemorrhage requiring aspiration. Others have reported local complications at the cutaneous puncture site and a cerebrovascular event.25 Of the five patients who died within 1 week of the procedure, two had established severe renal impairment before AS with a creatinine clearance of <50 ml/min (nos 14 and 16). The development of severe (fatal) hypoxaemia after AS in patient 10 has been reported previously.

No differences in haemodynamic or functional parameters were seen between patients who died within 1 week of the procedure (excluding patient 9 who stopped renal dialysis) and survivors. The only factors suggesting an adverse outcome were older age and a higher degree of functional renal impairment (table 3).

Current recommendations19–20 suggest four exclusion criteria for AS: (1) RAP >20 mm Hg, (2) SaO2 <90%, (3) predicted 1 year survival <40%, and (4) PVR >55 wood units/m2 (>4400 dyne*s/cm5). However, in our study patients with RAP ≤20 mm Hg (nos 9 and 13), SaO2 <90% on air before AS (nos 6, 9, 11, and 12), and a predicted 1 year survival of <40% (nos 9 and 13) showed no procedure related inverse outcome. None of our patients had PVR >55 wood units/m2 so we cannot comment on this criterion.

The high post-procedural mortality in previous studies has been attributed to the blade balloon technique which carries a greater risk of sepal laceration and fatal hypoxaemia but has a closure rate of only 3%.16 In an attempt to reduce procedural complications, the graded balloon dilatation technique is more often used despite the higher risk of spontaneous closure of the AS.11–18 In our study the graded balloon dilatation technique was associated with a spontaneous closure rate of 15% compared with 17% reported in the literature.25

CI measured by both the thermodilution and Fick methods significantly improved after AS. However, CI measured by thermodilution was significantly lower than the calculation based on the Fick method. This has been described in tricuspid regurgitation but was not found in primary pulmonary hypertension.17–18 As CI is important in the management and prognosis in PAH, this needs to be further evaluated.

Systemic oxygen transport is critical for the maintenance of adequate tissue oxygenation and optimal organ function.19–23 The significant post-procedural increase in SOT in our study indicates a potential for better tissue oxygenation, which may explain some of the improvements in symptoms and the overall outcome. However, AS is associated with a reduction in SaO2, and worsening mixed venous hypoxia is known to contribute to pulmonary vasoconstriction.26 A decrease in SaO2 below 75% after AS has been associated with a higher rate of mortality, but none of our patients had an SaO2 below 78% after the procedure (all received oxygen supplementation).

In the 91 published patients (including those in the present series), AS resulted in increases in CI of 24% and in SOT of 11%. However, 15 of the 91 patients (16%) died within 1 week of the procedure as a result of progressive hypoxia (n=8), progressive RHF (n=6), and arrhythmia (n=1). The overall 30 day mortality was 19% with two further patients dying from progressive heart failure and renal failure, respectively.25 In total, 45 patients were alive 2–96 months after the procedure without (H)LTx (49%) and 17 patients underwent (H)LTx after 2–19 months.19 In our study the longest survival time before AS with a creatinine clearance of <50 ml/min. (nos 14 and 16). The development of severe (fatal) hypoxaemia after AS in patient 10 has been reported previously.

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<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (years)</th>
<th>Cr Cl (ml/min)</th>
<th>6MWD (m)</th>
<th>RAP (mm Hg)</th>
<th>mPAP (mm Hg)</th>
<th>CI (l/min/m2)</th>
<th>SOT (ml/min/m2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors (n=12)</td>
<td>2M/10F</td>
<td>36 (10)</td>
<td>70 (16)</td>
<td>271 (87)</td>
<td>11 (6)</td>
<td>53 (8)</td>
<td>1.8 (0.5)</td>
</tr>
<tr>
<td>Deceased (n=4)</td>
<td>2M/2F</td>
<td>52 (8)</td>
<td>48 (21)</td>
<td>223 (29)</td>
<td>10 (5)</td>
<td>53 (89)</td>
<td>1.6 (0.3)</td>
</tr>
<tr>
<td>p&lt;0.05</td>
<td>p=0.01</td>
<td>p&lt;0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Values are mean (SD).**

Sex: M=male; F=female.

*p=0.05 p=0.01 p<0.05 NS NS NS NS NS NS NS NS

**Table 3** Comparison of short term outcome after atrial septostomy (AS)
without HLTx so far is 17 months (but we only started to perform AS in patients with PAH 2 years ago). We therefore cannot comment as to whether AS alters the short or medium term mortality in this high risk patient population.

In summary, balloon atrial septostomy is a therapeutic option in patients with severe PAH. It improves clinical and haemodynamic function and has the potential to influence the prognosis. However, it is associated with a significant risk of early post-procedure mortality. In our series this was more related to the underlying condition and comorbidity (significant renal dysfunction and increased age) of the patients than to the procedure itself. It is therefore possible that balloon septostomy should be considered at an earlier stage in the development of pulmonary hypertension, but this hypothesis needs further study. At present this procedure is undertaken only as a last resort in patients with severe PAH who are deteriorating on medical treatment (treatment refractory fluid retention or recurrent syncopal attacks as a result of reduced CO due to disease progression). The optimal timing of the procedure in patients with severe PAH has yet to be determined.

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