ASD and PH
close it or not?

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Zurich

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ASD and PH

Contents

- Background
- Results of ASD closure
- Pulmonary hypertension and ASD – with or without closure
- ASD closure in pts with PH
  - Technical considerations / modifications
  - Immediate and mid-term results
- Summary / Conclusion
ASD – natural course
mortality + incidence

Due to:

- RV failure +/- TR
- (Atrial) tachyarrhythmia
- Infections
- Pulmonary hypertension (~ 1/3, beginning with 3rd/4th decade)

Incidence of PH in adult ASD pts at time of closure 9 - 11%

Vogel et al., 1999
Balint et al., 2008
ASD – natural course survival – depending on PH

Gabriels et al., 2014
ASD and PH in adults

Engelfriet et al., 2007
ASD closure in children + adults

Echo parameters before/after closure

n = 112

Kaya et al., 2010
# ASD closure in adults

## Echo dimensions + ECG after closure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Procedure</th>
<th>1 Month</th>
<th>p Value</th>
<th>6 Months</th>
<th>p Value</th>
<th>1 Year</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTR (%)</td>
<td>49 ± 7</td>
<td>46 ± 7</td>
<td>&lt; 0.001*</td>
<td>47 ± 8</td>
<td>&lt; 0.001*</td>
<td>48 ± 7</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>RA overload on ECG</td>
<td>4/33 (12%)</td>
<td>3/36 (8.3%)</td>
<td>0.385</td>
<td>0/32</td>
<td>&lt; 0.001*</td>
<td>0/25</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>QRS axis</td>
<td>63 ± 33*</td>
<td>60 ± 28*</td>
<td>0.027</td>
<td>54 ± 26*</td>
<td>0.027</td>
<td>57 ± 21*</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>PR interval (ms)</td>
<td>181 ± 8</td>
<td>155 ± 2</td>
<td>&lt; 0.001*</td>
<td>151 ± 2</td>
<td>0.061</td>
<td>147 ± 2</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>125 ± 2</td>
<td>119 ± 2</td>
<td>0.001*</td>
<td>109 ± 1</td>
<td>&lt; 0.001*</td>
<td>104 ± 1</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>R wave in lead V₁ (mm)</td>
<td>2.5 ± 1.5</td>
<td>2.4 ± 1.7</td>
<td>0.769</td>
<td>2.3 ± 1.6</td>
<td>0.413</td>
<td>1.8 ± 1.3</td>
<td>0.413</td>
</tr>
<tr>
<td>RV size (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Four-chamber normal 26–43</td>
<td>45 ± 8</td>
<td>41 ± 6</td>
<td>0.003*</td>
<td>37 ± 5</td>
<td>&lt; 0.001*</td>
<td>37 ± 6</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>RVOTD (mm)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Normal 18–34</td>
<td>39 ± 7</td>
<td>34 ± 5</td>
<td>0.004*</td>
<td>33 ± 6</td>
<td>0.001*</td>
<td>33 ± 6</td>
<td>0.066</td>
</tr>
<tr>
<td>RA length (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal 34–49</td>
<td>52 ± 7</td>
<td>50 ± 6</td>
<td>0.081</td>
<td>47 ± 5</td>
<td>&lt; 0.001*</td>
<td>47 ± 6</td>
<td>0.027</td>
</tr>
<tr>
<td>Patients with PSM</td>
<td>21/36 (60%)</td>
<td>2/37 (5%)</td>
<td>&lt; 0.001*</td>
<td>4/33 (12%)</td>
<td>&lt; 0.001*</td>
<td>0/27</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Systolic PA pressure &gt;35 mm Hg</td>
<td>23/37 (62%)</td>
<td>17/38 (45%)</td>
<td>0.016*</td>
<td>9/33 (27%)</td>
<td>&lt; 0.001*</td>
<td>8/27 (29%)</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

*Veldtman et al., 2001*
ASD closure in children + adults

ECG after closure

Kaya et al., 2010
ASD closure in children + adults

NYHA functional classes after closure

Veldtman et al., 2001

Kaya et al., 2010
ASD closure in children + adults

Changes after closure

- Volume unloading of the RA and RV
- Better intra-atrial and intraventricular conduction properties
- Normalization of RV and RA dimensions
- Normalization of RV function (abnormal septal motion)
- Improvement of clinical status / exercise performance

- Progressive reduction of (estimated) systolic PA pressure
- Persistent elevation in rest systolic PA pressures in ~1/3 of adult pts

Kaya et al., 2010
Veldtman et al., 2001
ASD closure
Pre-Interventional work-up

Good correlation between

PA systolic pressure

estimated at echocardiography

and

at cardiac catheterization
(under general anesthesia)

Yong et al., 2009
ASD in adults

Association between sPAP and NYHA functional class

Engelfriet et al., 2007

n = 504
**ASD in adults**

**pulmonary artery pressure during exercise**

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<table>
<thead>
<tr>
<th></th>
<th>Control Subjects</th>
<th>ASD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\dot{V}O_2^{\text{max}}, \text{mL/min/kg}$</td>
<td>22.9±5.4</td>
<td>17.3±4.2†</td>
</tr>
<tr>
<td>(% predicted)</td>
<td>(87±20)</td>
<td>(75±13)†</td>
</tr>
<tr>
<td>$VT, \text{mL/min/kg}$</td>
<td>11.7±2.4</td>
<td>11.5±1.7</td>
</tr>
<tr>
<td>(% predicted $\dot{V}O_2^{\text{max}}$)</td>
<td>(44±7)</td>
<td>(48±8)</td>
</tr>
<tr>
<td>Maximum HR, beats/min</td>
<td>158±9</td>
<td>147±20</td>
</tr>
<tr>
<td>(% predicted)</td>
<td>(95±15)</td>
<td>(87±17)</td>
</tr>
<tr>
<td>$BR, \text{L/min}$</td>
<td>58±17</td>
<td>53±14</td>
</tr>
<tr>
<td>Peak exercise $\text{SaO}_2, %$</td>
<td>98±1</td>
<td>98±2</td>
</tr>
<tr>
<td>$\text{RVSPex, mm Hg}$</td>
<td>19±8</td>
<td>51±10†</td>
</tr>
</tbody>
</table>

_{Oelberg et al., 1998_}
ASD in adults
pulmonary artery pressure during exercise

Limited exercise capacity and exercise-induced PH

Possibly due to…
- **Elevated pulmonary vascular resistance**
- **Abnormal LV performance**
  - poorly recruitable pulmonary circulation under exercise
  - augmented left-to-right interatrial shunting
  - interventricular septal shift due to RV volume overload

\[ \text{Closed circles – ASD pts} \]
\[ \text{Open circles - controls} \]

*Oelberg et al., 1998*
ASD in adults
preoperative saturation (SpO2)

Preoperative parameters predicting postoperative PAH after ASD closure

After multivariate analysis:
- **room air SaO2** as a strong predictor for requiring postop anti-PAH medications

- **Sat > 93% no postoperative PAH**
  - shunt direction is dominantly left to right
  - pulmonary vasculature is still compliant
  - the defect can be safely closed

- **Sat < 93% PAH possible**
  - Careful approach for ASD closure
  - Fenestrated closure ??

*Park et al., 2016*
Development of PH in ASD pts
pathophysiological aspects

High pulmonary flow (+pressure)
=> endothelial damage + dysfunction

- loss of endothelial barrier function (release of growth factors + degradation of extracellular matrix)
- smooth muscle cell hypertrophy and proliferation in pulmonary vasculature
- Adherence and activation of platelets and leukocytes
- affected production of vasoconstrictors + vasodilators
- endothelin-1 and thromboxane
  > NO, intestinal vasoactive peptides, PG I 2

- not all pts with chronic volume overload will develop PAH
- multifactorial cause of PVD (genetic factors…)

Diller et al., 2007
Gabriels et al., 2014
Development of PH in ASD pts

risk factors

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>OR*</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>1.08</td>
<td>1.05 to 1.11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>2.4</td>
<td>1.1 to 5.7</td>
<td>0.0475</td>
</tr>
<tr>
<td>ASD size, mm</td>
<td>1.06</td>
<td>1.01 to 1.13</td>
<td>0.0284</td>
</tr>
<tr>
<td>NYHA class 3 or 4</td>
<td>4.6</td>
<td>2.1 to 10.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Atrial tachycardia</td>
<td>2.3</td>
<td>1.1 to 4.6</td>
<td>0.0193</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>5.8</td>
<td>2.3 to 14.5</td>
<td>0.0002</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.3</td>
<td>1.2 to 4.6</td>
<td>0.0154</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2.4</td>
<td>1.0 to 5.6</td>
<td>0.0453</td>
</tr>
<tr>
<td>Dilated left atrium</td>
<td>2.9</td>
<td>1.4 to 5.9</td>
<td>0.0044</td>
</tr>
<tr>
<td>At least moderate tricuspid regurgitation</td>
<td>6.7</td>
<td>3.1 to 14.6</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Multivariate analysis:**

1. Age
2. Female gender
3. ASD size
4. At least moderate TR

Yong et al., 2009
ASD and PH in adults
RV dysfunction depending on sPAP

Engelfriet et al., 2007
Abnormal left heart function after operation for atrial septal defect

Hywel Davies¹, G. Charles Oliver, William J. Rappoport, and Nikos Gazetopoulos
From Guy's Hospital, London S.E.1, U.K., and St. Joseph's Hospital, Denver, Colorado, U.S.A.

Post-operative data have been presented in seven patients with atrial septal defect. In five of them, residual patency of the atrial septum was found at cardiac catheterization, but in two the defect had been closed.

All showed evidence of 'left-sided dysfunction', expressed either as an increase in the pulmonary arterial wedge pressure or the left ventricular end-diastolic pressure or both. The reasons for these findings are not clear, though in several there were indications of impaired right ventricular compliance and possible transmission of raised right-sided pressures to the left side of the heart through a still patent atrial septum. This could not, however, be the mechanism in all cases, and dysfunction of the left ventricle has been seen in two patients in whom the defect was securely closed. The cause of this phenomenon in these selected cases remains obscure.
Occasional left heart failure after (surgical/interventional) ASD closure in elderly patients due to

- left ventricular diastolic dysfunction / restrictive disorder as a consequence of long-lasting changed loading conditions for the left ventricle («unloading»)

- and/or concomitant diseases like coronary artery disease

ASD closure
left ventricular dysfunction

ASD-balloon test occlusion

Ewert et al. 2001
Tomai et al, 2002
Schubert et al., 2005
Therapeutic options

- prophylactic medication consisting of iv diuretics and inotropic agents to prevent LV decompensation after ASD closure («preconditioning»)

- Reduction of left-to-right shunt with fenestrated ASD closure as an overflow relief for the restricted LV

Ewert et al. 2001
Schubert et al., 2005
n = 54 adult pts with ASD and moderate/severe PH for transcatheter ASD closure

<table>
<thead>
<tr>
<th>Baseline variables</th>
<th>RVSP &lt;60 mm Hg (n = 33)</th>
<th>RVSP ≥60 mm Hg (n = 6)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>61 (15)</td>
<td>54 (13)</td>
<td>0.31</td>
</tr>
<tr>
<td>Additional contributory causes of PAH*</td>
<td>7 (21)</td>
<td>3 (50)</td>
<td>0.16</td>
</tr>
<tr>
<td>NYHA ≥II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before closure</td>
<td>17 (52)</td>
<td>6 (100)</td>
<td>0.06</td>
</tr>
<tr>
<td>After closure</td>
<td>5 (15)</td>
<td>4 (67)</td>
<td>0.02</td>
</tr>
<tr>
<td>Atrial arrhythmia after closure</td>
<td>6 (18)</td>
<td>2 (33)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Balint et al., 2008
ASD closure in PH

results

Closure protocol for pts with severe PH and ASD

Preoperative determination of the degree of reversibility of PAH by

1. **Vasoreactor testing** with oxygen / NO / aerolized iloprost

   => **responder:** decrease in both PVR and pulmonary-to-systemic vascular resistance ratio (Rp/Rs) > 10%

2. **Attempted closure**

   => **responder:**
   
a) decrease of > 20% in the mPAP
   b) no decrease in the aortic pressure
   c) no worsening of signs and symptoms

*Huang et al., 2012*
ASD closure in PH

Results

15 adult pts with severe PH and ASD for transcatheter ASD closure

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>12 months</th>
<th>Change of post-operation 12 months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>87.2 ± 18.7</td>
<td>74.4 ± 12.8</td>
<td>-12.8 ± 11.9</td>
<td>0.074</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>51.6 ± 9.4</td>
<td>21.0 ± 3.8</td>
<td>-30.6 ± 7.0</td>
<td>0.001</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>7.4 ± 3.6</td>
<td>5.2 ± 1.3</td>
<td>-2.2 ± 3.4</td>
<td>0.224</td>
</tr>
<tr>
<td>PVR (Wood)</td>
<td>8.5 ± 1.8</td>
<td>2.9 ± 0.9</td>
<td>-5.6 ± 1.1</td>
<td>0.001</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>2.9 ± 0.7</td>
<td>3.2 ± 0.6</td>
<td>+0.3 ± 1.0</td>
<td>0.082</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>91.3 ± 5.2</td>
<td>93.4 ± 1.1</td>
<td>+2.1 ± 5.2</td>
<td>0.090</td>
</tr>
</tbody>
</table>

WHO functional class

Huang et al., 2012
ASD closure in PH

**results**

<table>
<thead>
<tr>
<th>Degree of PAH at Baseline</th>
<th>All</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients, n (%)</td>
<td>215</td>
<td>107</td>
<td>62</td>
<td>27</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>53.9 ± 15.7</td>
<td>47.2 ± 14.6</td>
<td>57.0 ± 14.5</td>
<td>63.6 ± 11.8</td>
<td>67.1 ± 11.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>157</td>
<td>78</td>
<td>40</td>
<td>20</td>
<td>19</td>
<td>0.2823</td>
</tr>
</tbody>
</table>

- Complete normalization of PASP in all pts with mild PAH
- 2/3 of pts with moderate PAH
- nearly 25% in pts with severe PAH

☑️ large reversible component to pulmonary vascular changes is common in ASD pts with PAH

*Yong et al., 2009*
ASD closure in «irreversible» PH results

1. 29 y female, severe (systemic) PH, large ASD, no shunt, NYHA class 3, iv prostacyclin for 4 years => PAP ½ systemic, LR-shunt 3:1 => successful ASD closure => after 8 years FU under amlodipin ½ systemic PAP, NYHA class 2

2. 38 y female, severe (systemic) PH, large ASD (20 mm), bidirectional shunt, PVR 8.8 WU, mild reagibility under vasoreactor testing, NYHA class 3 => iv prostacyclin for 18 months => PAP ½ systemic, PVR 2.8 WU, => successful ASD closure => under continued Bosentan therapy stable ½-systemic PAP, NYHA class 1

Frost et al., 2005
Schwerzmann et al., 2006
Partial ASD closure in PH with fenestrated devices

An atrial fenestration may be needed (mostly in elderly patients)

➢ as a decompression site in case of PAH crisis (for the right ventricle)

➢ as a decompression site for a restrictive left ventricle
Partial ASD closure in PH
with fenestrated devices

Perforation (with a 12 Fr dilator)

Perforation + dilatation

But these devices will show

a gradual spontaneous diminuinion and finally closing (after a
maximum time span of 12 months) of the fenestration
due to the memory properties of the nitinol

Amin et al., 2002
Peters et al., 2005
Kretschmar et al., 2010
Partial ASD closure in PH with fenestrated devices

Perforation + Suturing the margins

Perforation + stent implantation

⇒ Ensures a long(er)-lasting / persistent atrial fenestration (for pts with PAH)

Peters et al., 2005
Kretschmar et al., 2010
Skinner et al., 2013
If untreated, moderate + large ASDs may lead with time to PH (incidence in adulthood 9-11%)

Age, female gender, ASD size and at least moderate TR are the main risk factors for the development of PH

Early detection strategy and early closure of the defect (in childhood) is the best prophylaxis for PH and its complications

Lately detected ASDs in adults need a careful pre-interventional work-up concerning PH and diastolic LV function – saturation at rest, exercise testing, echo (RVSP, diastolic function…)}
ASD and PH

Summary / Discussion II

- ASD closure in adult pts with PH will lead in most of them to a
  - significant clinical improvement
  - significant and lasting reduction/normalization of PAP

- Pts with severe PH need a more extensive work-up with
  - vasodilator testing and/or test occlusion of the ASD
  - possibly medical pre-conditioning (prostacyclin) for later ASD closure

- Self-constructed fenestrated nitinol devices might serve as a pop-off ventile in pts with severe PH and/or LV dysfunction

⇒ Closing an ASD in pts with any degree of PH should be considered seriously in every patient with an individualized stepwise therapy regime
Thank you very much for your attention!

Oliver Kretschmar

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