Shaping the future of paediatric pulmonary arterial hypertension
Douwes, Johannes Menno

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CHAPTER 03b

Acute pulmonary vasodilator response in paediatric and adult pulmonary arterial hypertension: occurrence and prognostic value when comparing three response criteria

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**Abstract**

**Aims.** To assess the occurrence and prognostic value of acute vasodilator response (AVR) in paediatric vs. adult pulmonary arterial hypertension, and idiopathic/hereditary pulmonary arterial hypertension (iPAH/HPAH) vs. pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) using three different response criteria.

**Methods and results.** Ninety-nine PAH patients underwent AVR testing (37 children, 62 adults; 70 iPAH/HPAH, 29 PAH-CHD). Three response criteria from clinical practice were used to define AVR. The number of responders was evaluated separately in subgroups based on age, diagnosis, and presence of a non-restrictive post-tricuspid shunt. Numbers of responders varied importantly using the different criteria but were always higher in iPAH/HPAH, compared with PAH-CHD. The number of responders did not differ between paediatric and adult iPAH/HPAH. No responders were identified in patients with a post-tricuspid shunt. Acute vasodilator response was associated with improved survival using all three criteria. Low baseline mean right atrial pressure (mRAP) was associated with improved survival in adults (P<0.001). High baseline mean pulmonary arterial pressure (mPAP)/mean systemic arterial pressure (mSAP) and pulmonary vascular resistance (PVR)/systemic vascular resistance (SVR) were associated with worse survival, statistically independent from age, diagnosis, and the presence of a post-tricuspid shunt.

**Conclusion.** The proportion of patients with AVR highly depends on the used criteria, but did not differ between paediatric and adult iPAH/HPAH. Current response criteria are not suitable for patients with a post-tricuspid shunt. In both children and adults without post-tricuspid shunts, AVR was associated with improved survival independent of the used criteria. Nevertheless, prognostic value in the individual patient was limited. Baseline mRAP showed a good correlation with survival for adult PAH patients, but not for children. High baseline mPAP/mSAP and PVR/SVR was associated with worse prognosis independent from age, diagnosis, or the presence of a post-tricuspid shunt.
**Introduction**

Pulmonary arterial hypertension (PAH) is a disease characterized by progressive pulmonary vascular remodelling and severe elevations of pulmonary vascular resistance (PVR) and pressure, ultimately leading to right ventricular failure and death. Pulmonary arterial hypertension can occur idiopathically (iPAH), hereditary (HPAH), or associated with underlying conditions, such as congenital heart defects (PAH-CHD). According to international guidelines, acute pulmonary vascular response to vasodilator challenge during right heart catheterization (acute vasodilator response (AVR)) is an important factor in the evaluation of PAH. Treatment with calcium channel blockers (CCB) is only recommended in patients with an acute response (responders). Furthermore, the presence of AVR has been reported to be associated with better survival. Finally, in patients with CHD and flow-associated PAH, AVR testing is used to assess progression of the pulmonary vascular disease to evaluate operability of the heart defect.

Although AVR has important clinical consequences, its definition remains controversial. Three criteria are generally used: the criteria according to Barst, Rich, and Sitbon. The Rich criteria, the first commonly used criteria for adults, were proposed in 1992. In 2005, Sitbon et al. suggested new criteria for adult iPAH, based on a retrospective evaluation of an adult iPAH patient cohort. In international guidelines, these Sitbon criteria are currently recommended for adult PAH patients, but not for children. In children, the Barst criteria are generally used. In iPAH, the proportion of patients with AVR has been reported to be higher in children (42–56% according to the Barst criteria) than in adults (12 – 26% according to the Rich criteria). In general, 5 – 17% of adult iPAH patients have AVR according to the Sitbon criteria. However, due to the use of different response criteria, it is difficult to directly compare the data of these studies.

Data on AVR are derived predominantly from iPAH/HPAH patients. It is unclear whether the response criteria are suitable for other subclasses of PAH. The applicability of these response criteria is particularly questionable in patients with PAH-CHD and post-tricuspid shunts. Their haemodynamic physiology prohibits qualifying for acute responder according to these criteria, irrespective of the progression of the pulmonary vascular disease.

The purpose of this study was to assess potential differences in the proportion of patients with AVR between children and adults, iPAH/HPAH and PAH-CHD, and patients with or without non-restrictive post-tricuspid shunt according to the three criteria in use. Furthermore, the prognostic value of AVR and isolated haemodynamic parameters was studied.

**Methods**

**Patients**

We retrospectively reviewed cardiac catheterization data of adult and paediatric (aged 0.3 – 18 years) patients with iPAH/HPAH and PAH-CHD. Patients were catheterized at the
University Medical Center Groningen, national referral centre for paediatric PAH, and the VU University Medical Center Amsterdam, between January 1990 and July 2008. Diagnosis of PAH was defined as mean pulmonary arterial pressure (mPAP) >25 mmHg, with a pulmonary capillary wedge pressure ≤15 mmHg and PVR >3 Woods units. At our PAH referral centre, all PAH-CHD patients had advanced PAH and were considered to be inoperable. Only patients with complete invasive haemodynamic data, including acute pulmonary vasodilator challenge, were included. In patients who had undergone more than one catheterization, the first available was selected. Patients with a non-restrictive ventricular septal defect, complete atrioventricular septal defect, patent ductus arteriosus, or monoventricular heart with unobstructed pulmonary blood flow were identified as patients with a post-tricuspid shunt. Isolated atrial septal defects were defined as pre-tricuspid shunts. Patients without shunt, with a corrected shunt, or with a pre-tricuspid shunt were assigned to the group of patients without post-tricuspid shunt. During the study period, patients were treated in congruence with evolving guidelines eventually resulting in the ‘ESC guidelines on diagnosis and treatment of PAH’. All patients had regular standardized follow-up visits at the centres, referral centres for paediatric, and adult PAH. Our Institutional Medical Ethics committee waived the need for patient consent in this study, because of its retrospective nature and because individual patients were not identified.

**Baseline evaluation**

Baseline evaluation included medical history, World Health Organization (WHO) functional class, and the first complete right cardiac catheterization. In children, cardiac catheterization was performed under general anaesthesia, and in adults no general anaesthesia was used. Baseline haemodynamic measurements included mean right atrial pressure (mRAP), mPAP, mean systemic arterial pressure (mSAP), mean pulmonary capillary wedge pressure and pulmonary arterial, pulmonary venous, mixed systemic venous and systemic arterial saturations, and oxygen pressures. When pulmonary veins could not be reached, pulmonary venous saturation was assumed 98%. Pulmonary and systemic blood flows were determined using Fick’s method and indexed for body surface area (Qpi and Qsi). Oxygen consumption (VO₂) was estimated using two methods: (i) for patients <7 years of age VO₂ = 1.39 × Height (cm) + 0.84 × Weight(kg) 235.7 and (ii) for patients >7 years of age by Lafarge and Miettinen. Pulmonary and systemic vascular resistance indexes (PVRi and SVRi) were calculated by dividing the pulmonary or systemic arterial to venous pressure difference by Qpi or Qsi, respectively.

**Acute response testing**

In this period of evolving diagnostic guidelines, pulmonary vasodilator response was tested using several different drugs: inhaled nitric oxide (NO; dosage 40 – 80 ppm in Groningen, 20 ppm in Amsterdam), 100% oxygen (O₂), the combination of NO and 100% O₂, intravenous prostacyclin (4 – 20 ng/kg/min), CCB (10 mgr nifedipine) and sildenafil (50 mgr). The presence of acute response was evaluated according to three generally used criteria:
1. Barst criteria, 1986: decrease in mPAP of ≥20%, unchanged or increased cardiac index, and decreased or unchanged pulmonary to systemic vascular resistance ratio (PVR/SVR); 4,9
2. Rich criteria, 1992: decrease in mPAP and PVR of ≥20%; 5
3. Sitbon criteria, 2005: decrease in mPAP of ≥10 mmHg reaching a mPAP value of ≤40 mmHg and an increased or unchanged cardiac output. 3,10

The change of a haemodynamic variable (in absolute value or percentage) during vasodilator challenge was calculated by subtracting baseline values from values measured during vasodilator challenge, resulting in negative values for variables which decreased and positive values for variables which increased during vasodilator challenge.

In case of subsequent vasodilator tests with different drugs, acute response was evaluated separately for each test. In all patients, the best-reached values at vasodilator challenge were selected.

**Statistical analyses**

Patients were subsequently assigned to different subgroups for the purpose of three comparisons: (i) children vs. adults (age groups), (ii) iPAH/HPAH vs. PAH-CHD (diagnosis groups), and (iii) patients with non-restrictive post-tricuspid shunt vs. those without post-tricuspid shunt (Figure 1).

**Figure 1:**

A flow chart showing the composition of the subgroups that patients were assigned to for the purpose of three comparisons: (i) children vs. adults (age groups), (ii) idiopathic pulmonary arterial hypertension/hereditary pulmonary arterial hypertension vs. pulmonary arterial hypertension associated with congenital heart disease (diagnosis groups), and (iii) patients with non-restrictive post-tricuspid shunt vs. those without post-tricuspid shunt.
Statistical analysis was performed using SPSS statistics (version 16; SPSS 2007, Chicago, IL, USA). Data are presented as mean ± SD or number (percentage) of patients. The number of responders to acute pulmonary vasodilator testing and haemodynamic values (at baseline and after vasodilator challenge) were compared between the three sets of subgroups using Fishers’ exact tests (number of responders) and independent samples t-tests (continuous normally distributed baseline variables, haemodynamic changes, and best-reached values).

Survival was evaluated starting from haemodynamic evaluation. To identify continuous haemodynamic variables associated with survival, haemodynamic variables were assessed by univariate Cox regression analysis. Taking into account the size of the study group, multivariate survival analyses were done in a conservative way. In sequential multivariate Cox regression analyses, the covariates age-groups, diagnosis, and the presence of a post-tricuspid shunt were separately added to the haemodynamic variables that were significantly associated with survival in the univariate analyses. Survival was depicted using Kaplan – Meier curves for all patients, the respective subgroups, responders vs. non-responders according to all three criteria and haemodynamic variables found to be associated with survival in Cox regression analyses. Log-rank tests were used to analyse the difference in survival in the respective subgroups depicted in the Kaplan – Meier curves. Because of the small number of patients with follow-up beyond 7 years, the survival curves and log-rank tests were truncated at 7 years of follow-up. All statistical tests were two-sided and P-values < 0.05 were considered significant.

**Results**

**Study group**

Ninety-nine patients were included in the study (37 children, 62 adults). There were 70 iPAH/HPAH and 29 PAH-CHD patients. There were 20 patients with a post-tricuspid shunt (Table 1). Vasodilating agents used for AVR testing included inhaled NO (n = 73), 100% O₂ (n = 61), NO and 100% O₂ (n = 53), intravenous prostacyclin (n = 34), sildenafil (n = 18), and CCB (n = 4). The majority of patients (n = 81) were tested with more than one vasodilating agent. All results remained unchanged after exclusion of patients who were tested only with 100% O₂ (n = 7).

**Number of acute responders**

The number of acute vasodilator responders varied greatly when using the different response criteria (Figure 2; P < 0.001). There was no difference in number of responders between children and adults. Furthermore, sub-analyses performed to improve comparability with previous studies showed no difference in number of responders between children and adults with iPAH/HPAH (Barst criteria: 13 vs. 24%, P = 0.35; Rich criteria: 29 vs. 28%, P = 1.00; Sitbon criteria: 8 vs. 13%, P = 0.71, respectively).

In the different diagnosis subgroups, there were 14 (Barst criteria; 20%), 20 (Rich criteria; 29%) and 8 (Sitbon criteria; 11%) acute responders in the iPAH/HPAH group. In the PAH-CHD group,
there was one responder without a post-tricuspid shunt (11%). No responders were identified in patients with a post-tricuspid shunt.

According to all three criteria, the presence of AVR depends on the decrease of mPAP (mmHg or %) and/or PVRi (%). These variables did not differ at baseline between children and adults. In PAH-CHD patients without a post-tricuspid shunt (n = 9), mPAP decreased during vasodilator challenge (maximal mPAP change: -3.3 ± 6.1 mmHg; in percentage: -6.1 ± 13.8%; Table 2). In PAH-CHD patients with a post-tricuspid shunt, mPAP did not significantly decrease at any vasodilator challenge.

### Survival

In the total study group, 1-, 2-, and 5-year survival was 94, 88, and 72%, respectively, with a median follow-up time of 3.8 years (range 0.0 – 14.3; Table 1). No patients were lost to follow-up. Data did not allow for adjusting the survival analyses for treatment. No difference in survival could be demonstrated between children vs. adults and iPAH/HPAH vs. PAH-CHD patients in this series. Patients with a post-tricuspid shunt tended to have better survival than patients without post-tricuspid shunt, although not reaching statistical significance in this series (Figure 3A).

### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Children</th>
<th>Adults</th>
<th>p-value* No post-tricuspid shunt</th>
<th>Post-tricuspid shunt</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=99)</td>
<td>(n=37)</td>
<td>(n=62)</td>
<td>(n=79)</td>
<td>(n=20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at right heart catheterization (yrs)</td>
<td>19.9 ± 18.1</td>
<td>8.0 ± 5.3</td>
<td>40.8 ± 12.6</td>
<td>&lt;0.001</td>
<td>16.9 ± 16.7</td>
<td>25.6 ± 19.6</td>
</tr>
<tr>
<td>Follow-up time (yrs)</td>
<td>3.8 (0.0-14.3)</td>
<td>2.8 (0.0-14.3)</td>
<td>4.0 (0.0-9.6)</td>
<td>0.932</td>
<td>3.9 (0.0-12.5)</td>
<td>3.1 (0.0-14.3)</td>
</tr>
<tr>
<td>Diagnoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iPAH/HPAH</td>
<td>70 (71)</td>
<td>24 (65)</td>
<td>46 (74)</td>
<td>0.366</td>
<td>70 (89)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PAH-CHD</td>
<td>29 (29)</td>
<td>13 (35)</td>
<td>16 (26)</td>
<td></td>
<td>9 (11)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Sex Male</td>
<td>38 (38)</td>
<td>13 (35)</td>
<td>25 (40)</td>
<td>0.637</td>
<td>30 (38)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>WHO- functional class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4 (4)</td>
<td>3 (8)</td>
<td>1 (2)</td>
<td>0.291</td>
<td>3 (4)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>II</td>
<td>20 (21)</td>
<td>7 (19)</td>
<td>13 (22)</td>
<td>17 (22)</td>
<td>3 (15)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>56 (58)</td>
<td>19 (51)</td>
<td>37 (63)</td>
<td>42 (55)</td>
<td>14 (70)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>16 (17)</td>
<td>8 (22)</td>
<td>8 (14)</td>
<td>14 (18)</td>
<td>2 (10)</td>
<td></td>
</tr>
<tr>
<td>Post-tricuspid shunt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>79 (80)</td>
<td>28 (76)</td>
<td>51 (82)</td>
<td>0.448</td>
<td>79 (100)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20 (20)</td>
<td>9 (24)</td>
<td>11 (18)</td>
<td></td>
<td>20 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Values are in mean ± SD, median (range) or N (%).
*Comparison between children and adults or no post-tricuspid shunt and tricuspid-shunt, respectively, with t-test or Chi-square as appropriate.
In iPAH/HPAH patients, survival tended to be better in responders vs. non-responders, although statistical significance was not reached (Barst criteria: P = 0.11; Rich criteria: P = 0.09; Sitbon criteria: P = 0.50). We subsequently analysed survival of responders vs. non-responders in all patients without post-tricuspid shunt (iPAH/HPAH and PAH-CHD). Patients with a post-tricuspid shunt were excluded from this analysis, because no responders were identified in this group and they showed better survival. Survival tended to be better in responders than in non-responders without post-tricuspid shunt according to each of the three criteria, although statistical significance was not reached (Barst criteria: P = 0.08; Rich criteria: P = 0.06; Sitbon criteria: P = 0.38; Figure 3B). In sub-analysis, these results persisted in the subgroups of children and adults without post-tricuspid shunt. In children, the Barst and Sitbon responders had excellent survival (100%), although due to small numbers the difference in survival compared with non-responders did not reach statistical significance (P = 0.23 and 0.32, respectively).

Figure 2:

The number of acute pulmonary vasodilator responders according to the three criteria in use, in children vs. adults with idiopathic pulmonary arterial hypertension (iPAH)/hereditary pulmonary arterial hypertension (HPAH), iPAH/HPAH vs. pulmonary arterial hypertension associated with congenital heart disease, and patients without vs. with post-tricuspid shunt, respectively. Data presented as percentage of patient group (%) and patient numbers (indicated in bars). Comparison between groups performed using Fisher’s exact test.
Table 2: Hemodynamic characteristics

<table>
<thead>
<tr>
<th>Hemodynamics at baseline</th>
<th>All patients</th>
<th>Children</th>
<th>Adults</th>
<th>p-value*</th>
<th>No post-tricuspid shunt</th>
<th>Post-tricuspid shunt</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=99)</td>
<td>(n=37)</td>
<td>(n=62)</td>
<td>(n=79)</td>
<td>(n=20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aorta saturation (%)</td>
<td>92 ± 7</td>
<td>93 ± 8</td>
<td>92 ± 6</td>
<td>0.658</td>
<td>94 ± 5</td>
<td>85 ± 9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean right atrial pressure (mmHg)</td>
<td>7 ± 4</td>
<td>6 ± 4</td>
<td>7 ± 5</td>
<td>0.319</td>
<td>7 ± 5</td>
<td>5 ± 2</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mmHg)</td>
<td>56 ± 19</td>
<td>55 ± 19</td>
<td>57 ± 19</td>
<td>0.537</td>
<td>52 ± 15</td>
<td>75 ± 22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean systemic arterial pressure (mmHg)</td>
<td>80 ± 19</td>
<td>64 ± 15</td>
<td>90 ± 14</td>
<td>&lt;0.001</td>
<td>80 ± 18</td>
<td>80 ± 24</td>
<td>0.901</td>
</tr>
<tr>
<td>mPAP/mSAP</td>
<td>0.7 ± 0.3</td>
<td>0.9 ± 0.3</td>
<td>0.6 ± 0.2</td>
<td>&lt;0.001</td>
<td>0.7 ± 0.3</td>
<td>0.9 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary blood flow index (l/min/m2)</td>
<td>2.5 ± 1.0</td>
<td>2.7 ± 1.0</td>
<td>2.4 ± 1.0</td>
<td>0.184</td>
<td>2.5 ± 0.9</td>
<td>2.7 ± 1.1</td>
<td>0.407</td>
</tr>
<tr>
<td>Systemic blood flow index (l/min/m2)</td>
<td>2.7 ± 1.1</td>
<td>3.0 ± 1.3</td>
<td>2.5 ± 0.9</td>
<td>0.021</td>
<td>2.5 ± 0.9</td>
<td>3.2 ± 1.6</td>
<td>0.071</td>
</tr>
<tr>
<td>Pulmonary vascular resistance index (WU.m2)</td>
<td>23 ± 14</td>
<td>21 ± 12</td>
<td>24 ± 16</td>
<td>0.284</td>
<td>21 ± 12</td>
<td>31 ± 20</td>
<td>0.036</td>
</tr>
<tr>
<td>Systemic vascular resistance index (WU.m2)</td>
<td>31 ± 14</td>
<td>22 ± 10</td>
<td>37 ± 12</td>
<td>&lt;0.001</td>
<td>32 ± 13</td>
<td>28 ± 15</td>
<td>0.196</td>
</tr>
<tr>
<td>PVR/VR</td>
<td>0.8 ± 0.6</td>
<td>1.0 ± 0.7</td>
<td>0.7 ± 0.4</td>
<td>0.003</td>
<td>0.7 ± 0.5</td>
<td>1.2 ± 0.7</td>
<td>0.004</td>
</tr>
<tr>
<td>During vasodilator testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mPAP maximal change (mmHg)</td>
<td>-5 ± 7</td>
<td>-3 ± 7</td>
<td>-6 ± 7</td>
<td>0.188</td>
<td>-6 ± 7</td>
<td>1 ± 6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(%)</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>best reached</td>
<td>52 ± 20</td>
<td>51 ± 21</td>
<td>52 ± 20</td>
<td>0.906</td>
<td>46 ± 16</td>
<td>76 ± 21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVRi maximal change (WU.m2)</td>
<td>-7 ± 6</td>
<td>-4 ± 5</td>
<td>-8 ± 7</td>
<td>0.012</td>
<td>-6 ± 5</td>
<td>-9 ± 11</td>
<td>0.293</td>
</tr>
<tr>
<td>(%)</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qsi maximal change (l/min/m2)</td>
<td>-30 ± 22</td>
<td>-25 ± 25</td>
<td>-32 ± 19</td>
<td>0.124</td>
<td>-32 ± 20</td>
<td>-21 ± 26</td>
<td>0.047</td>
</tr>
<tr>
<td>mPAP/mSAP maximal change absolute</td>
<td>-0.1 ± 0.1</td>
<td>-0.1 ± 0.1</td>
<td>-0.1 ± 0.1</td>
<td>0.785</td>
<td>-0.1 ± 0.1</td>
<td>-0.0 ± 0.1</td>
<td>0.207</td>
</tr>
<tr>
<td>best reached</td>
<td>0.7 ± 0.3</td>
<td>0.8 ± 0.3</td>
<td>0.6 ± 0.2</td>
<td>&lt;0.001</td>
<td>0.6 ± 0.3</td>
<td>0.9 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVR/VR maximal change absolute</td>
<td>0.6 ± 0.3</td>
<td>0.6 ± 0.3</td>
<td>0.6 ± 0.3</td>
<td>0.003</td>
<td>0.6 ± 0.4</td>
<td>0.9 ± 0.5</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Values are in mean ± SD or N (%).

*Comparison between children and adults or no post-tricuspid shunt and tricuspid-shunt, respectively, with t-test mPAP/mSAP, pulmonary to systemic arterial pressure ratio; PVR/SVR, pulmonary to systemic vascular resistance ratio; mPAP, mean pulmonary arterial pressure; PVRi, pulmonary vascular resistance index; WU, woods units.
In Cox regression analyses, lower mPAP/mSAP and PVR/SVR, both at baseline and during vasodilator testing, were associated with improved survival, where the analyses suggest that outliers might have determined the results in this survival analysis. Cox regression analyses showed that these associations were statistically independent from age groups, diagnosis groups, and the presence of a post-tricuspid shunt (Table 3). There was no statistical interaction between age groups, diagnosis groups, and the presence of a post-tricuspid shunt. However, in multivariate analyses of baseline mPAP/mSAP and PVR/SVR including the presence of a post-tricuspid shunt, the post-tricuspid shunt had an independent association with survival (HR 3.8 P = 0.073 and HR 5.9 P = 0.025, respectively). Therefore, and because of the physiological importance of the presence of such post-tricuspid shunt for mPAP/mSAP and PVR/SVR ratios, the associations of mPAP/mSAP and PVR/SVR with survival, as depicted in Kaplan–Meier curves (Figure 4), were stratified for the presence of a post-tricuspid shunt.

(A) Subgroups: Kaplan–Meier survival curves comparing survival of adults vs. children, idiopathic pulmonary arterial hypertension/ hereditary pulmonary arterial hypertension vs. pulmonary arterial hypertension associated with congenital heart disease, and post-tricuspid shunt vs. no post-tricuspid shunt. (B) Response: Kaplan–Meier survival curves comparing survival of responders vs. non-responders according to the Barst, Rich, and Sitbon criteria in patients without post-tricuspid shunt.
Table 3. Cox Regression Analyses

<table>
<thead>
<tr>
<th></th>
<th>Analysis 1</th>
<th>Analysis 2</th>
<th>Analysis 3</th>
<th>Analysis 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR† (95% CI)</td>
<td>p-value</td>
<td>HR† (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>PVR/SVR baseline</td>
<td>1.1 (1.0-1.2)</td>
<td>0.002</td>
<td>1.1 (1.0-1.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>maximal change</td>
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<td>0.725</td>
<td>1.0 (0.9-1.1)</td>
<td>0.746</td>
</tr>
<tr>
<td>best reached</td>
<td>1.1 (1.0-1.3)</td>
<td>0.004</td>
<td>1.2 (1.0-1.3)</td>
<td>0.005</td>
</tr>
<tr>
<td>mPAP/mSAP baseline</td>
<td>1.2 (1.0-1.4)</td>
<td>0.048</td>
<td>1.2 (1.0-1.5)</td>
<td>0.045</td>
</tr>
<tr>
<td>maximal change</td>
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<td>1.0 (0.7-1.3)</td>
<td>0.764</td>
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<td>best reached</td>
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<td>0.089</td>
<td>1.2 (1.0-1.4)</td>
<td>0.082</td>
</tr>
</tbody>
</table>

Analysis 1: univariate Cox regression analyses of baseline, maximal change, and best-reached PVR/SVR and mPAP/mSAP.
Analysis 2: multivariate Cox regression analysis including age groups.
Analysis 3: multivariate Cox regression analysis including diagnosis groups.
Analysis 4: multivariate Cox regression analysis including post-tricuspid shunt.

mPAP/mSAP, pulmonary to systemic arterial pressure ratio; PVR/SVR, pulmonary to systemic vascular resistance ratio; CI, confidence interval.

†HR, hazard ratio per 0.1 change in PVR/SVR and mPAP/mSAP.

Figure 4:

Kaplan Meier curves stratified for post-tricuspid shunt-specific tertiles of pulmonary vascular resistance (PVR)/systemic vascular resistance (SVR) or mean pulmonary arterial pressure (mPAP)/mean systemic arterial pressure (mSAP), comparing the first two tertiles (PVR/SVR < 0.73 and mPAP/mSAP < 0.76 for patients without post-tricuspid shunt and PVR/SVR < 1.48 and mPAP/mSAP < 0.98 for patients with post-tricuspid shunt) with the third tertile of PVR/SVR and mPAP/mSAP (PVR/SVR > 0.73 and mPAP/mSAP > 0.76 for patients without post-tricuspid shunt and PVR/SVR > 1.48 and mPAP/mSAP > 0.98 for patients with post-tricuspid shunt).

The prognostic mRAP cut-off values of the ESC guidelines (mRAP <8 mmHg and >15 mmHg, respectively) were highly associated with survival in adults (P < 0.001). In children, these mRAP cut-off values were not associated with survival, since the mRAP in children in our
series almost never reached such high values (81% of children had an mRAP <8 mmHg, only one child had an mRAP >15 mmHg). Cox regression analyses show that mRAP was associated with survival in adults (HR 1.19, P <0.01), but not in children (HR 1.02 P = 0.82).

Discussion

In contrast to general belief, no difference was observed in the proportion of patients identified as responder to AVR testing between children and adults with iPAH/HPAH. Since the number of responders appears to be highly dependent on the used criteria, previously reported higher numbers of responders in paediatric PAH compared with adults may be due to the use of different criteria in different studies and the lack of previous comparative studies. In the current study, the highest number of responders in all subgroups was identified using the Rich criteria, followed by the Barst and Sitbon criteria. Most responders were seen in the iPAH/HPAH group. In contrast, no responders were observed in patients with PAH-CHD associated with a post-tricuspid shunt. Responders tended to have improved survival compared with non-responders in all patients without a post-tricuspid shunt. Mean right atrial pressure was only associated with survival in adults, not in children due to low occurrence of increased mRAP in this age group. High baseline PVR/SVR and mPAP/mSAP were associated with poorer survival, statistically independent from age groups, diagnosis, and the presence of a post-tricuspid shunt. No other haemodynamic variable at baseline or at vasodilator challenge could be identified to be associated with survival.

Our observation that the number of responders was highly dependent on the used criteria, the PAH diagnosis, and the presence of a post-tricuspid shunt implies that care should be taken in comparing the numbers of responders between different studies. By identifying responders in the different age and diagnosis groups and by using all three currently used criteria, we were able to make more appropriate comparisons. In our series, the highest number of responders was found in patients with iPAH/HPAH. Previously, the proportion of responders in iPAH/ HPAH patients was reported to be 30% higher in children than in adults. However, using the same criteria in both groups, we found no difference in AVR between children and adults with iPAH/HPAH.

In adult patients with iPAH/HPAH, we observed similar percentages of responders (13 – 28%) as those previously reported for adult iPAH/HPAH using both the Rich criteria (12 – 26%)\textsuperscript{5,10} and Sitbon criteria (5 – 17%).\textsuperscript{12,13} However, in children with iPAH/ HPAH, we observed lower numbers of responders (13, 29, and 8% using Barst, Rich, and Sitbon criteria, respectively) compared with those initially reported in children with iPAH/HPAH (Barst criteria 42 – 56%).\textsuperscript{4,9} These lower percentages are in line with more recently reported proportions of 10 – 15% in children with iPAH/HPAH.\textsuperscript{3,18} Taken together, we conclude that the proportion of paediatric iPAH/HPAH patients that have an AVR is not larger than in adults.

The lower number of responders in patients with PAH-CHD compared with patients with iPAH/HPAH may be due either to a difference in vascular disease characteristics or to a dif-
ference in circulatory physiology between these two disease entities. First, it is important to realize that PAH-CHD patients, presenting at PAH referral centres, are in general a selection of patients with advanced vascular disease. In contrast, patients who are diagnosed early with CHD are likely to have less-advanced vascular disease and may more frequently show an acute vasoreactive response to vasoactive agents, indicating the possibility of surgical closure of the defect. The lower number of responders in PAH-CHD in this series may therefore not be generalized to all PAH-CHD patients.

In order to specifically address the different circulatory physiologies in patients with PAH-CHD, we evaluated patients with and those without post-tricuspid shunt. In patients with a post-tricuspid shunt, no acute vasodilator responders could be identified with the used criteria, since mPAP did not decrease at vasodilator challenge. In these patients, the pulmonary and systemic circulations are connected at ventricular or arterial level. Therefore, pulmonary arterial pressures can only fall in conjunction with a decrease in systemic arterial pressures, and as a result cannot meet current response criteria requiring a decrease in mPAP, regardless the condition of the pulmonary vascular bed. Consequently, criteria based on mPAP are not suitable for this patient group. However, PVR may be an important factor in these patients. Modified criteria, focussed on a decrease in PVR with increasing Qpi, may allow for identifying responders in patients with post-tricuspid shunt. Recently, Budts et al.\textsuperscript{19} suggested that in PAH-CHD patients with advanced vascular disease who do not qualify for surgical correction of the defect, acute response to NO, defined as decrease in PVR, indicates a therapeutic window for selective pulmonary vasodilator treatment. Furthermore, AVR testing can be helpful in assessing the possibility of heart defect closure in PAH-CHD patients with pre-tricuspid shunts, even in those with longstanding PAH.\textsuperscript{20} However, validated criteria for such assessment are lacking. Our observation that survival of responders is better in all PAH patients without post-tricuspid shunts suggests that the criteria may be of prognostic value not only in iPAH/HPAH, but also in PAH-CHD patients without a post-tricuspid shunt.

Survival in iPAH/HPAH patients seemed to be better in responders compared with non-responders according to all three response criteria. This trend confirms previous studies reporting improved survival in responders.\textsuperscript{4,10} The lack of statistical significance in our study may be due to relatively small patient numbers. However, the fact that statistical significance was not reached in this study with 70 iPAH/HPAH patients challenges the value of acute response as a prognostic tool in the individual patient. An initial positive response does not guarantee better outcome. Sitbon et al.,\textsuperscript{10} therefore, strongly recommended that responders who are treated with CCB should be closely monitored and one should not hesitate to treat them as non-responders when the effect of CCB does not persist.

The Barst and Sitbon criteria seemed to more specifically select PAH patients with improved survival (one death in the responders, based on these criteria; 7 and 11%, respectively), compared with the Rich criteria (three deaths in the responders; 14%). This is in congruence with the findings of Sitbon et al.\textsuperscript{10} that only a smaller portion of the Rich responders have a
sustained long-term treatment response to oral CCB and improved survival. The difference between the three criteria may be due to their design. In contrast to Rich criteria, the Barst and Sitbon criteria require an unchanged or increased cardiac output to identify a patient as a responder. These criteria exclude patients in whom the fall in mPAP (and consequent fall in PVR) is not due to a pulmonary vasodilator response, but caused by a reduction in pulmonary blood flow.

In order to identify PAH patients who have a preferential pulmonary vascular response, the ratio between mean pulmonary and systemic pressures and resistances (mPAP/msAP and PVR/SVR), representing the pulmonary response corrected for the systemic response, may be useful. This is especially true for patients with a post-tricuspid shunt, in whom the systemic and pulmonary circulation are directly connected. Previous reports show that lower baseline mPAP/msAP and PVR/SVR were associated with improved survival. In our study, we confirmed this association statistically, where analysis suggested that the correlation of mPAP/msAP and PVR/SVR (at baseline and during vasodilator challenge) with survival was driven by the highest values for mPAP/msAP and PVR/SVR. Therefore, the prognostic value of mPAP/msAP and PVR/SVR may be restricted to the proportion of patients with the highest values for these ratios.

Baseline mRAP was demonstrated to be a parameter highly associated with survival in adult PAH patients. In children, this parameter had no prognostic value, since their mRAP was rarely much increased.

Limitations of this study include the relatively small patient numbers, which impede us from making more definitive statements on prognostic values of AVR. However, in the rare disease of PAH, data on the numbers and definition of acute pulmonary vasodilator responders are limited, particularly in children and patients with PAH-CHD. This study offers important information on these issues, and provides a basis for extending the applicability of current criteria to a growing group of PAH patients, other than adults with iPAH/HPAH. Further, in this study conditions during catheterization differed between children and adults (general anaesthesia vs. sedation) and VO2 was assumed instead of measured. However, these methods reflect real-life clinical practice and will therefore have minimal effect on the clinical relevance of the study. Furthermore, different vasodilating drugs were used to perform acute vasodilator tests, whereas current guidelines recommend using NO and avoiding the use of CCB. The use of one vasodilator, for example NO, in all study patients might have been more ideal. However, the three criteria for defining AVR were designed using also different pulmonary vasodilators and currently no data are available demonstrating that using inhaled NO for identification of AVR is superior to other vasodilators in predicting response to CCB or prognosis. Finally, individualized treatment data of the included patients was not available. However, since all patients were treated according to the ESC guidelines for pulmonary hypertension, treatment was regarded not a confounding factor between patient groups.
In conclusion, the proportion of PAH patients that has an acute pulmonary vasodilator response depends highly on the used criteria. In this comparative study, using similar criteria, no statistically significant difference in numbers of responders was found between children and adults with iPAH/HPAH. According to the current criteria, the number of responders was highest in iPAH/HPAH and absent in patients with PAH-CHD associated with a post-tricuspid shunt. The currently used acute response criteria are not suitable for PAH-CHD patients with a post-tricuspid shunt, but may be useful as a prognostic tool in PAH-CHD patients without a post-tricuspid shunt. All three response criteria seem to select responders with improved survival, although the prognostic value in the individual patient may be limited. Baseline mPAP/mSAP and PVR/SVR were associated with survival, statistically independent from age groups, diagnosis groups, and the presence of a post-tricuspid shunt. The baseline mRAP was strongly associated with survival in adults, but not in children.
References


