CHAPTER 4
Clinical characterization of pediatric pulmonary hypertension: complex presentation and diagnosis

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ABSTRACT

Objectives
To describe the clinical presentation of pediatric pulmonary arterial hypertension (PAH) and the intricacies in how to classify pediatric PAH according to the Venice classification.

Study design
Children (n=63), seen at a national referral center for pediatric PAH, underwent diagnostic work-up for diagnosis of pulmonary hypertension (PH) and associated conditions and for assessment of the explanatory role of associated conditions for the PH. Subsequently, PH was classified.

Results
In 18 patients (29%) no associated conditions were identified; they were classified as having idiopathic PAH. In 45 patients (71%) ≥1 associated conditions were detected: congenital heart defects (CHD, n=40), connective tissue disease (CTD, n=2), disorders of respiratory system and/or hypoxemia (RSH, n=17) and chronic thromboembolic (CTE) disease (n=1). Patients were classified according to the condition judged primarily explanatory for the PH. In 11 of 45 patients with associated conditions, the PH was not sufficiently explained by these conditions; these patients were classified as idiopathic-like PAH. In 17 of 40 cases of CHD and 9 of 17 cases of RSH, these conditions were not sufficiently explanatory for the PH. Syndromal abnormalities were remarkably frequent (43%). Ultimately, classification revealed: idiopathic(-like) PAH (n=29; 46%), PAH-CHD (n=23; 37%), PAH-CTD (n=2; 3%), PH-RSH (n=8; 12%), and CTEPH (n=1; 2%).

Conclusion
Pediatric PH frequently presents with associated conditions and syndromal abnormalities. However, detailed evaluation of this complex presentation reveals that associated conditions are not always explanatory for the PH.
INTRODUCTION

Pulmonary hypertension (PH) is defined by an increased mean pulmonary arterial pressure of >25 mmHg at rest or >30 mmHg during exercise. The Venice classification categorizes PH into 5 classes on the basis of shared similarities in pathophysiological mechanisms, clinical course, and therapeutic options. Class 1 comprises pulmonary arterial hypertension (PAH). Classes 2 to 5 consist of PH associated with the following conditions: pulmonary venous hypertension, disorders of respiratory system and/or hypoxemia (RSH), thromboembolic disease, and a variety of conditions termed as miscellaneous. PAH distinguishes itself from the other 4 classes of PH histologically by characteristic pulmonary vascular lesions, and clinically by its chronic progressive course and response to advanced medication. PAH is subclassified into idiopathic PAH (either sporadic or familial), and PAH associated with various underlying conditions.1,2

Pediatric PAH is a serious fatal disease, which requires treatment with specific advanced medication. This is in contrast to other pediatric PH (sub)classes, in which relief of underlying conditions is the first aim. The Venice classification has proven to be essential for the diagnosis and management of patients with PH, because prognosis and treatment strategy heavily depend on the (sub)class of PH.2 Therefore, it is important to diagnose associated conditions accurately, to assess their explanatory role in the development of PH accurately, and to subsequently classify PH accurately. However, no studies exist which describe the complex clinical decisions surrounding this diagnostic process. Data on the clinical presentation of pediatric PH is scarce and limited to studies on the outcome of children after treatment with certain medications. Thorough information concerning the diagnostic process prior to the start of treatment is lacking.3-6

The objectives of this study were to describe the clinical presentation of pediatric PH in a cohort of children seen at a national referral center for pediatric PAH and to describe the intricacies in how to classify pediatric PH according to the Venice classification.

METHODS

Patients
In the Netherlands, pediatric cardiologic care is centralized within 8 university medical centers. Patients with suspected PH are seen by pediatric cardiologists at any of the 8 centers for initial diagnostics. The care for pediatric patients with PAH is united in a national Network for Diagnosis and Treatment of Pediatric PAH. This network includes all 8 university medical centers, one of which serves as an expert center. All pediatric patients suspected to have PAH are referred to this expert center for diagnostic work-up and initiation of therapy. Also, all patients with PH suspected to be caused by thromboembolic disease, miscellaneous disorders, or both (Venice classes 4 and 5, respectively) are referred to the expert center. In contrast, patients with other forms of PH, caused by pulmonary venous hypertension or caused by RSH, such as bronchopulmonary dysplasia, (Venice classes
2 and 3, respectively) are not systematically referred to the expert center. The expert center has served as a referral center for pediatric PAH since 1993. In the Netherlands, the importance of centralizing the care for pediatric patients with PAH, because of the complexity of the disease and the small numbers of patients, has been recognized relatively early. Therefore, the expert center evolved into the national referral center for pediatric PAH, and a national network was installed during the late 1990s.

Between 1993 and 2007, a cohort of 63 children with suspected PAH was referred to the expert center. Patient data was entered in a database registry with informed consent from the parents/caregivers. Institutional review board approval was obtained for the registry of these patients.

**Study assessments**

At presentation at the expert center, all children underwent diagnostic work-up in order to diagnose PH, to identify associated conditions, and to assess the explanatory role of the associated conditions for the PH. Subsequently, PH was classified according to the Venice classification. Diagnostic work-up included standardized Doppler echocardiography and cardiac catheterization in order to confirm the diagnosis of PH and to systematically assess the heart for cardiac anomalies, right and left ventricular function, and to exclude pulmonary venous obstruction, left heart disease, or both. In addition, acute pulmonary vasodilator response was tested using inhaled oxygen, nitric oxide and/or intravenous prostacyclin. Responders were identified according to criteria as defined by Barst. Diagnosis of PH was made invasively during cardiac catheterization and measurement of a mean pulmonary arterial pressure >25 mmHg and pulmonary capillary wedge pressure <15 mmHg at rest in 57 patients. In the 6 remaining patients, cardiac catheterization data was not available. Clinical instability (n=4) and positive response of PH to adequate treatment of the associated condition (obstructive breathing, n=2) were reasons for not performing cardiac catheterization in these patients. Of these 6 patients, in 3 patients who had systemic-to-pulmonary shunt related PAH, a right-to-left shunt was measured echocardiographically, establishing Eisenmenger syndrome physiology. In the other 3 patients, the presence of PH was established by measurement of a maximum systolic tricuspid regurgitant velocity >2.8 m/s, according to criteria as defined by McQuillan et al. Diagnostic evaluation for associated conditions was performed uniformly, according to protocol, in all patients, and included assessment of chest radiography, complete blood and platelet count, thyroid function, thrombotic status, HIV serology, overnight oxymetry, arterial blood gas, pulmonary perfusion scan, and screening for connective tissue disease. In selected patients, additional blood clotting studies, polysomnography, pulmonary function testing, and thoracic computed tomography (CT) scan were performed. From 2002, incident and prevalent patients with idiopathic PAH were screened for bone morphogenetic protein receptor type 2 (BMPR2) gene mutations. Clinical patient characteristics included symptoms, transcutaneous oxygen saturation (TcSO2), and World Health Organization functional class.
**Statistical analysis**

Data are presented as mean ± SD or medians and ranges, as appropriate. To analyze differences in baseline characteristics between PH (sub)classes, one-way ANOVA with Bonferroni post-hoc testing (TcSO2, hemodynamics) and Kruskal-Wallis followed by Mann-Whitney post-hoc testing with Bonferroni correction (symptoms, World Health Organization functional class) were performed. For one-way ANOVA and Kruskal-Wallis testing, (sub)classes comprising only one patient or only one available assessment were excluded. P-values <0.05 were considered to be significant.

**RESULTS**

**Patients and baseline characteristics**

Exercise-induced dyspnea was the most common presenting symptom (98%; Table 1). Syncope occurred in 8 patients (13%). One patient had no symptoms on presentation and was referred for screening because of a diastolic murmur and Noonan syndrome. The murmur originated from a mild pulmonary regurgitation jet with high maximal velocity.

**Identification of associated conditions and classification of PH**

In 45 patients (71%) ≥1 associated conditions were detected: 1 associated condition in 30 (48%) and 2 associated conditions in 15 patients (24%). Associated conditions consisted of congenital heart defects (CHD) in 40 patients (63%), disorders of respiratory system and/or hypoxemia (RSH) in 17 patients (27%), connective tissue disease (CTD) in 2 patients (3%), and chronic thromboembolic disease (CTE) in 1 patient (2%; Figure 1). In 18 patients (29%), no associated conditions were identified, and these patients were classified as having idiopathic PAH (Figure 1). In these patients, intrinsic pulmonary vascular disease was considered to be explanatory for the PH. Patients with >1 associated condition were classified according to the associated condition judged to be primarily explanatory for the PH. In 11 of the 45 patients (25%) in whom associated conditions were detected, PH was not sufficiently explained by these conditions, although a possible role for these conditions in the PH disease progression cannot be excluded (CHD, n=9; CHD and concomitant RSH n=1; RSH, n=1). Therefore, PH was considered to be caused by additional intrinsic pulmonary vascular disease, and these 11 patients were classified as idiopathic-like PAH (Figure 1), a recently proposed new PAH subclass.9
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients n=63</th>
<th>iPAH n=29</th>
<th>PAH-CHD n=23</th>
<th>PAH-CTD n=2</th>
<th>PH-RSH n=8</th>
<th>CTEPH n=1</th>
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<tbody>
<tr>
<td><strong>Age at presentation at referral center</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>5.8 (0.1; 17.4)</td>
<td>5.0 (0.04; 15.8)</td>
<td>6.9 (0.05; 17.4)</td>
<td>6.9 (6.8; 7.1)</td>
<td>0.8 (0.5; 13.9)</td>
<td>15.7</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>24 (38)</td>
<td>13 (45)</td>
<td>6 (26)</td>
<td>1 (50)</td>
<td>4 (50)</td>
<td>0</td>
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<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dyspnea</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>- exercise induced</td>
<td>62 (98)</td>
<td>28 (97)</td>
<td>23 (100)</td>
<td>2 (100)</td>
<td>8 (100)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>- at rest</td>
<td>16 (25)</td>
<td>4 (14)</td>
<td>6 (26)</td>
<td>1 (50)</td>
<td>5 (63)</td>
<td>0</td>
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<td>2 (7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>Syncope</td>
<td>8 (13)</td>
<td>7 (30)</td>
<td>1 (4) *</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>TcSO2 (%)</td>
<td>91 ± 7</td>
<td>94 ± 5</td>
<td>89 ± 7 †</td>
<td>87</td>
<td>88 ± 9</td>
<td>98</td>
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<tr>
<td>WHO class I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>17 (27)</td>
<td>8 (28)</td>
<td>6 (26)</td>
<td>0</td>
<td>3 (38)</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>30 (47)</td>
<td>13 (45)</td>
<td>12 (52)</td>
<td>1 (50)</td>
<td>3 (38)</td>
<td>1 (100)</td>
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<tr>
<td>IV</td>
<td>15 (24)</td>
<td>7 (24)</td>
<td>5 (22)</td>
<td>1 (50)</td>
<td>2 (24)</td>
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<td><strong>Hemodynamics</strong></td>
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<tr>
<td>n=57</td>
<td></td>
<td>n=29</td>
<td>n=20</td>
<td>n=1</td>
<td>n=6</td>
<td>n=1</td>
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<tr>
<td>Responder</td>
<td>9 (14)</td>
<td>7 (24)</td>
<td>1 (4)</td>
<td>1 (50)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>mRAP (mmHg)</td>
<td>7 ± 4</td>
<td>7 ± 4</td>
<td>7 ± 4</td>
<td>8</td>
<td>7 ± 3</td>
<td>4</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>52 ± 20</td>
<td>55 ± 17</td>
<td>54 ± 20</td>
<td>61</td>
<td>25 ± 5 †</td>
<td>75</td>
</tr>
<tr>
<td>mPAP/mSAP</td>
<td>0.9 ± 0.3</td>
<td>0.9 ± 0.3</td>
<td>1.0 ± 0.1</td>
<td>1.10</td>
<td>0.6 ± 0.2 †</td>
<td>0.96</td>
</tr>
<tr>
<td>CI (L/min/m2)</td>
<td>2.8 ± 1.1</td>
<td>2.8 ± 0.8</td>
<td>2.8 ± 1.5</td>
<td>3.6</td>
<td>2.9 ± 0.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Qpix/CI</td>
<td>1.2 ± 0.9</td>
<td>1.0 ± 0.2</td>
<td>1.1 ± 0.6</td>
<td>0.80</td>
<td>1.1 ± 0.1</td>
<td>1.2</td>
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<tr>
<td>PVRix (WU.m2)</td>
<td>18.4 ± 13.4</td>
<td>19.9 ± 12.3</td>
<td>20.1 ± 15.1</td>
<td>19.5</td>
<td>4.2 ± 1.3 †</td>
<td>14.3</td>
</tr>
<tr>
<td>PVR/SVR</td>
<td>1.0 ± 0.6</td>
<td>1.0 ± 0.6</td>
<td>1.0 ± 0.7</td>
<td>1.40</td>
<td>0.3 ± 0.2</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Data presented as n (%), median (range) and/or mean ± SD.

PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; iPAH, idiopathic(-like) PAH; PAH-CHD, PAH associated with congenital heart defects; PAH-CTD, PAH associated with connective tissue disease; PH-RSH, PH associated with disorders of respiratory system and/or hypoxemia; CTEPH, chronic thromboembolic PH.

TcSO2, transcutaneous oxygen saturation; Responder, acute pulmonary vasodilator testing responder; mRAP, mean right atrial pressure; mPAP, mean pulmonary artery pressure; mPAP/mSAP, ratio between mean pulmonary and systemic arterial pressure; CI, cardiac index; Qpix/CI, ratio between pulmonary and systemic blood flow; PVRix, pulmonary vascular resistance index; PVR/SVR, ratio between pulmonary vascular and systemic vascular resistance; WU, Woods units.

iPAH vs PAH-CHD: * Syncope P=0.06 (Fisher’s exact test) † TcSO2 P=0.02 ‡ PH-RSH vs iPAH and PH-RSH vs PAH-CHD: mPAP P<0.01, PAP/SAP P<0.03, PVRix P<0.04
Table 2. Congenital heart defects

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>(%)</th>
<th>Closed shunt/ corrected defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASDI</td>
<td>2</td>
<td>(5)</td>
<td></td>
</tr>
<tr>
<td>ASDII</td>
<td>4</td>
<td>(10)</td>
<td></td>
</tr>
<tr>
<td>ASDII + PAPVR</td>
<td>1</td>
<td>(2)</td>
<td>1</td>
</tr>
<tr>
<td>VSD</td>
<td>6</td>
<td>(15)</td>
<td>1</td>
</tr>
<tr>
<td>VSD ± PDA ± ASD</td>
<td>5</td>
<td>(14)</td>
<td>1</td>
</tr>
<tr>
<td>PDA</td>
<td>4</td>
<td>(10)</td>
<td>2</td>
</tr>
<tr>
<td>cAVSD</td>
<td>8</td>
<td>(20)</td>
<td>5</td>
</tr>
<tr>
<td>cAVSD ± PDA ± ASD</td>
<td>1</td>
<td>(2)</td>
<td>1</td>
</tr>
<tr>
<td>TGA (without VSD)</td>
<td>2</td>
<td>(5)</td>
<td>2</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>1</td>
<td>(2)</td>
<td>1</td>
</tr>
<tr>
<td>Complex</td>
<td>5</td>
<td>(13)</td>
<td></td>
</tr>
<tr>
<td>Coarctation of aorta</td>
<td>1</td>
<td>(2)</td>
<td>1</td>
</tr>
</tbody>
</table>

ASDI, primum atrial septal defect; ASDII, secundum atrial septal defect; PAPVR, partially anomalous pulmonary venous return; VSD, ventricular septal defect; PDA, patent ductus arteriosus; cAVSD, complete atrioventricular septal defect; TGA, transposition of great arteries; Complex, single ventricle (n=3); VSD + PDA + PAPVR (n=1); PDA + major aortopulmonary collateral arteries (n=1)

**Congenital heart defects**

Associated CHD constituted a great variety of defects (Table 2). Of the 40 patients with a CHD, 27 had an isolated CHD and 13 had concomitant RSH (Figure 1).

Of the 27 patients with an isolated CHD, 13 were classified as “classic Eisenmenger syndrome” (Figure 1). Classic Eisenmenger syndrome was defined as PAH due to an uncorrected post-tricuspid systemic-to-pulmonary shunt defect (e.g. ventricular septal defect; VSD), leading to increased pulmonary vascular resistance, reversal of the shunt, and subsequent hypoxemia.\(^{10}\) Five other patients were classified as “PAH-CHD after post-tricuspid shunt closure” (Figure 1). They had undergone previous adequate closure of a hemodynamically significant post-tricuspid shunt defect after which PAH persisted or returned (complete atrioventricular septal defect, cAVSD, n=3, VSD + patent ductus arteriosus (PDA) n=1, truncus arteriosus n=1). Correction of their CHD had failed to prevent development of progressive pulmonary vascular disease. Median age at correction of their CHD was 3.0 years (range 0.3-7.6). In one of these patients, an ASD had to be created, because of clinical deterioration 1 year after corrective surgery. Another 9 patients were classified as idiopathic-like PAH (Figure 1). In these 9 patients, the CHD was hemodynamically insignificant, and consequently not sufficiently explanatory for the PH. Therefore, additional intrinsic pulmonary vascular disease was suspected. Of these patients, 3 had a pre-tricuspid shunt defect (ASDII), 3 had a small originally restrictive post-tricuspid shunt defect (VSD n=2, spontaneously closed PDA in first year of life n=1), 2 patients had undergone a neonatal arterial switch operation for transposition of great arteries (median age 8 days, range 3-12), and 1 patient had undergone successful neonatal correction of coarctation of aorta without residual pulmonary venous obstructive lesions (age 14 days).

In 5 of the 13 patients with a CHD and concomitant RSH (Figure 1) persistent, severe PAH with right-to-left shunting through a post-tricuspid heart defect developed in the first
weeks to months of life (median 0.2 years, range 0.05-0.4). Because this is much earlier than usual for development of PAH due to systemic-to-pulmonary shunt, this group was named “accelerated PAH-CHD” (Figure 1), suggesting additional intrinsic pulmonary vascular disease. All these 5 patients also had RSH consisting of associated obstructive upper airway breathing. However, despite adequate treatment of these respiratory disorders with improved ventilation, PH persisted, indicating that the obstructive breathing was not primarily explanatory for the PH. In 7 other patients with CHD and RSH consisting of obstructive upper airway breathing, the CHD was regarded as not sufficiently explanatory for the PH, because treatment of the obstructive breathing reversed the PH (Figure 1). Therefore, obstructive upper airway breathing was judged to be primarily explanatory for the PH, and these 7 patients were classified as having PH-RSH. Two of these patients had a small pre-tricuspid shunt (ASDII, ASDI), and 5 patients had undergone previous closure of their CHD (complete atrioventricular septal defect, n=3; VSD, n=1; PDA, n=1; median age at CHD correction 0.9 years, age range 0.3-2.9 years). In the other, remaining patient, neither the CHD (small ASDII, corrected at 14.9 years of age), nor the RSH consisting of obstructive upper airway breathing (obstructive sleep apnea syndrome) was sufficiently explanatory for the PH (Figure 1). Adequate treatment of the obstructive breathing did not reverse the PH. Therefore, this patient was classified as having idiopathic-like PAH.

**Disorders of respiratory system and/or hypoxemia**

RSH included obstructive upper airway breathing disorders in 15 patients (88%), and interstitial lung disease caused by CTD in 2 patients (12%). Obstructive upper airway breathing disorders consisted of obstructive sleep apnea syndrome (n=3) or disordered breathing due to enlarged adenoid, tonsils and tongue, and/or small upper airways (n=12). Obstructive upper airway breathing disorders were identified by measurement of nocturnal desaturations and blood gas analysis revealing compensated hypercapnia, in combination with the presence of obstructive upper airway anatomy. When PH could be reversed with improved ventilation and oxygen therapy (e.g. during anesthesia for cardiac catheterization) or removal of the upper airway obstruction, the respiratory disorder was considered to be explanatory for the PH. Measures to improve ventilation and remove upper airway obstruction included nocturnal continuous positive airway pressure treatment, adenotonsillectomy, removal of nasogastric tubes and installation of a percutaneous endoscopic gastric (PEG)-catheter, or simply by growth of the child and consequent enlargement of the upper airways.

Of the 15 patients with obstructive upper airway breathing disorders, 13 had concomitant CHD and 2 had isolated respiratory disease (Figure 1). The latter 13 patients were described in the previous section. Of the 2 patients with an isolated respiratory disorder, 1 patient was accordingly classified as having PH-RSH caused by upper airway obstructive breathing. In the other patient, however, obstructive upper airway breathing was not the explanation for the PH. Therefore, this patient was classified as having idiopathic-like PAH (Figure 1).
Figure 1. Associated conditions and PH classification.

CHD, congenital heart defects; RSH, disorders of respiratory system and/or hypoxemia; CTD, connective tissue disease; CTE, chronic thromboembolic disease; "explanatory +", explanatory for pulmonary hypertension; "explanatory –", not sufficiently explanatory for pulmonary hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension, PAH-CHD, PAH associated with congenital heart defects with systemic-to-pulmonary shunt; PAH-CTD, PAH associated with connective tissue disease; PH-RSH, PH associated with disorders of respiratory system and/or hypoxemia; CTE-PH, chronic thromboembolic PH.
**Connective tissue disease**
In 2 patients, interstitial lung disease was confirmed with thoracic CT scan (Figure 1). In 1 patient neonatal-onset multisystem inflammatory disease (NOMID) syndrome was diagnosed, and in the other patient there was strong clinical suspicion for the presence of CTD, although additional blood analyses were not conclusive. Adequate treatment of the hypoxia and hypoxemia by improved ventilation and oxygen therapy did not reverse PH. Therefore, PAH due to CTD was concluded (PAH-CTD) (Figure 1).

**Chronic thromboembolic disease**
In 1 patient, with a ventriculoatrial drain because of congenital hydrocephalus, the diagnosis of CTE-PH was established with pulmonary perfusion scanning followed by selective angiography (Figure 1).

**PH classes and characteristics**
After assessing the explanatory role of each of the associated conditions to the development of PH in the individual patient, classification of PH revealed: idiopathic or idiopathic-like PAH in 29 patients (46%), PAH-CHD in 23 patients (37%), PAH-CTD in 2 patients (3%), PH-RSH in 8 patients (12%), and CTEPH in 1 patient (2%) (Figure 1).

The most common presenting symptom in all PH (sub)classes was exercise-induced dyspnea (Table 1). Syncope tended to be more frequent in patients with idiopathic(-like) PAH (P=0.06). TcSO2 was significantly lower in patients with PAH-CHD (P=0.02). Mean pulmonary arterial pressures (P<0.01) and pulmonary vascular resistance index (P=0.04) were significantly lower in patients with PH-RSH than in patients with idiopathic(-like) PAH and PAH-CHD.

**Genetic defects and syndromal abnormalities**
Screening for BMPR2 gene mutations was performed in 19 of the 29 patients with idiopathic(-like) PAH. Three patients (16%) had a BMPR2 gene mutation, of whom 1 had familial and 2 had sporadic idiopathic PAH.

In addition, syndromal abnormalities were encountered in 27 other patients (43%). The most common chromosomal abnormality was Down syndrome (n=13, 21%). Other specific syndromal abnormalities included Noonan (n=2, 3%), velocardiofacial (n=2, 3%), Jacobsen (n=1, 1.6%), 1p36 deletion (n=1, 1.6%), and neonatal-onset multisystem inflammatory disease syndrome (n=1, 1.6%). In 7 patients (11%), clinical dysmorphic features and/or psychomotor retardation without chromosomal abnormalities were observed. These patients were classified as having undefined syndromes. The distribution of these patients over the different PH subclasses is depicted in Figure 2.
DISCUSSION

In our series, pediatric PH was associated with ≥1 underlying conditions in approximately 75% of the children. However, these associated conditions, including CHD, RSH and CTD, were not always the explanation for the PH. In 25% of the children in whom an associated condition was identified, this condition was not primarily explanatory for the PAH, suggesting additional intrinsic pulmonary vascular disease. Ultimately, almost half of the children were classified as either idiopathic or idiopathic-like PAH. Syndromal abnormalities frequently co-occurred with pediatric PH (43% of all patients).

Congenital heart defects

In our series, CHD was the most common associated condition (n=40, 62%). However, thorough description of anatomic and hemodynamic features of the CHD, including location, size, direction, state, and timing of repair of the shunt substantiated that the PH was insufficiently explained by the CHD alone in 17 of the 40 patients (43%). Of these 17 patients, idiopathic-like PAH was diagnosed in 10, and concomitant RSH was explanatory for the PH in 7. CHD which were insufficiently explanatory for the PH included pre-tricuspid and small, originally restrictive post-tricuspid shunt defects, as well as corrected shunt defects.

In uncorrected pre-tricuspid shunt defects, development of irreversible PAH occurs in only 10-20% of adult patients, mainly in their 3rd or 4th decade. In children with isolated pre-tricuspid shunt defects, development of irreversible PH is extremely unusual. The
same holds for patients with small restrictive hemodynamically insignificant post-tricuspid shunt defects. In these cases, the pulmonary vasculature has not been subjected to systemic arterial pressures, and pulmonary-to-systemic blood flow often remains <1.5. In addition, in patients with transposition of the great arteries (without VSD) who undergo corrective surgery at neonatal age, PH usually does not develop as a result of increased pulmonary blood flow. However, the combination of neonatally corrected transposition of the great arteries and unexplained PAH is a rare but known combination, suggesting additional intrinsic pulmonary vascular disease in this specific population. A comparable situation applies to patients with coarctation of the aorta who undergo neonatal correction without any residual left heart lesions, in whom PAH develops afterwards. In our series of patients with such CHD and without other explanatory associated conditions, additional intrinsic pulmonary vascular disease was suspected, and therefore they were classified as having idiopathic-like PAH.

The Venice classification offers guidelines for the subclassification of CHD in PAH-CHD. These guidelines, however, are not sufficient for defining subsets of CHD on the basis of shared circulatory pathophysiology. Therefore, refinements for the subclassification of CHD were recently proposed. Our series of patients, with a diverse range of neonatally corrected to uncorrected pre and post-tricuspid shunt defects, demonstrates the need for these refinements.

Disorders of respiratory system and/or hypoxemia

Although this study describes pediatric patients referred for suspected PAH, RSH and especially obstructive upper airway breathing disorders were the second largest group of associated conditions in our series. These disorders occurred frequently in the setting of Down syndrome. Children with Down syndrome may have an anatomical predisposition because of midface hypoplasia, small upper airways, and macroglossia. A nasogastric tube for tube-feeding in infancy and enlarged tonsils or adenoid may aggravate obstructive breathing and PH due to additional mechanical narrowing of the upper airways and/or, in the case of nasogastric feeding, aspiration and consequent ventilation perfusion mismatch. Moreover, in these children hypotonia may lead to hypoventilation and nocturnal desaturations, and obesity may induce a form of Pickwickian syndrome. PH-RSH, in our series due to obstructive upper airway breathing in all patients, was characterized by relatively favorable hemodynamics and a relatively benign course. In contrast to PH in children with PAH, PH in this subclass resolved in most children after relieving the airway obstruction. Furthermore, in contrast to decreased survival in PAH, we observed no deaths in children with PH-RSH during follow-up. These findings underscore the importance of a thorough diagnostic work-up in children with PH, because an adequate diagnosis may dictate therapeutic strategy and outcome. The outcome of these pediatric patients also strongly contrasts with that of adults with PH-RSH. In adults, PH-RSH frequently occurs in the setting of chronic obstructive lung disease and these patients obviously have a more dismal outcome.
Genetic defects and syndromal abnormalities

BMPR2 gene defects were encountered in 3 (16%) of the 19 tested children with idiopathic(-like) PAH. This is in line with a previous study in 18 pediatric patients with idiopathic PAH reporting different genetic defects of the Transforming Growth Factor-beta pathway in 22% of the cases, half of which consisted of BMPR2 gene mutations. In addition, syndromal abnormalities were encountered in a remarkably high number of patients (43%). Down syndrome was the most common (21%). The increased incidence of PH in patients with Down syndrome is well known. As observed in our series, these patients may have different potential causes for PH, such as CHD, upper airway obstruction, pulmonary hypoplasia, and increased susceptibility for pulmonary vascular disease. In patients such as these with CHD and increased susceptibility for pulmonary vascular disease, screening for PH and early correction of the CHD should be considered in order to prevent development of PAH.

An interesting subset of 4 patients with Down syndrome and 1 patient with 1p36 deletion syndrome developed PH in the first months of life in the presence of a CHD, with right-to-left shunt, and obstructive upper airway breathing. We named this subset “accelerated PAH-CHD”. In these patients, extremely high pulmonary vascular resistance and right-to-left shunting through the heart defect was already present in the first weeks of life and persisted thereafter. In these patients, a failure of postnatal adaptation and remodeling of the pulmonary vascular bed may have contributed to this specific presentation of PAH and CHD. Although the obstructive upper airway breathing may have accounted partly for the PH, the PH remained progressive, even after measures to relieve upper airway obstruction. This observation is in line with previous reports which suggest higher susceptibility for PH in patients with Down syndrome.

The high prevalence of syndromal abnormalities in pediatric patients with PH could indicate the presence of unidentified genetic mutations leading to increased intrinsic susceptibility for pulmonary vascular disease via pathways that are currently unknown. Documentation of these clinical associations in combination with the developments in genetic analysis techniques such as genome-wide arrays, may lead to identification of such pathways.

This study has limitations. In 6 of 63 patients cardiac catheterization was not performed, due to clinical instability or positive response of PH to treatment of obstructive breathing. However, in 3 of these 6 patients, echocardiography unambiguously established the diagnosis of Eisenmenger syndrome, and in the other 3 patients obvious high maximal systolic tricuspid regurgitant velocity determined the presence of PH. Next, it is important to realize that this study cannot provide epidemiological data on the relative frequencies of the PH classes in the pediatric age group, such as PH associated with pulmonary venous congestion or with RSH, since these patients are not systematically referred to the expert center. Consequently, patient numbers for these PH classes are not representative for the total population and certain subclasses of PH, such as bronchopulmonary dysplasia, were not observed. In contrast, although not designed to answer epidemiological questions, this study does provide valuable data on the distribution of associated conditions in
pediatric PAH. Finally, this study describes the complexity in diagnosing and classifying PH in pediatric patients. Due to this complexity, classification may have been limited by arbitrary judgment. Nevertheless, these complex decisions are precisely those which clinicians are faced with in daily practice. We have therefore attempted to elucidate these decisions as systematically as possible.

In conclusion, pediatric PH is characterized by a complex clinical presentation. Associated conditions may be identified in the majority of cases. However, these associated disorders are not necessarily explanatory for the PH, indicating the presence of additional intrinsic pulmonary vascular disease in certain patients. In the assessment of CHD, careful attention must be paid to the circulatory physiology of the shunt in order to judge its explanatory role in the development of PH. Syndromal abnormalities are frequent in pediatric patients with PH, suggesting a possible genetic role in the development of PH.

For the general pediatrician it is important to be aware of PAH in children at risk for the disease, such as patients with Down syndrome and CHD, since PAH is a serious fatal disease which requires specific treatment. When echocardiography reveals PH, careful diagnostic work-up is required in order to identify associated conditions including obstructive breathing and CHD, and to define their explanatory roles in the PH. Patients with suspected PAH should be referred to centers with expert knowledge on pediatric PAH.
REFERENCES


