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Pediatric Pulmonary Hypertension in the Netherlands
Epidemiology and Characterization During the Period 1991 to 2005

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Background—Incidence and prevalence rates for pediatric pulmonary hypertension (PH) and pulmonary arterial hypertension (PAH) are unknown. This study describes the nationwide epidemiological features of pediatric PH in the Netherlands during a 15-year period and the clinical course of pediatric PAH.

Methods and Results—Two registries were used to retrospectively identify children (0–17 years) with PH. Overall, 3263 pediatric patients were identified with PH due to left heart disease (n=160; 5%), lung disease/hypoxemia (n=253; 8%), thromboembolic disease (n=5; <1%), and transient (n=2691; 82%) and progressive (n=154; 5%) PAH. Transient PAH included persistent PH of the newborn and children with congenital heart defects (CHD) and systemic-to-pulmonary shunt, in whom PAH resolved after successful shunt correction. Progressive PAH mainly included idiopathic PAH (n=36; iPAH) and PAH associated with CHD (n=111; PAH-CHD). Pulmonary arterial hypertension associated with CHD represented highly heterogeneous subgroups. Syndromes were frequently present, especially in progressive PAH (n=60; 39%). Survival for PAH-CHD varied depending on the subgroups, some showing better and others showing worse survival than for iPAH. Survival of children with Eisenmenger syndrome appeared worse than reported in adults. For iPAH and PAH-CHD, annual incidence and point prevalence averaged, respectively, 0.7 and 4.4 (iPAH) and 2.2 and 15.6 (PAH-CHD) cases per million children. Compared to studies in adults, iPAH occurred less whereas PAH-CHD occurred more frequently.

Conclusions—Pediatric PH is characterized by various age-specific diagnoses, the majority of which comprise transient forms of PAH. Incidence of pediatric iPAH is lower whereas incidence of pediatric PAH-CHD is higher than reported in adults. Pediatric PAH-CHD represents a heterogeneous group with highly variable clinical courses. **(*Circulation*. 2011;124:1755-1764.)**

Key Words: pulmonary hypertension ■ pediatric ■ epidemiology ■ incidence ■ prevalence

Pulmonary hypertension (PH) is a pathophysiological condition defined by an increased mean pulmonary arterial pressure of ≥25 mm Hg at rest. Pulmonary hypertension can develop from various underlying diseases, which are categorized into 5 groups, summarized by the clinical classification of PH.[1] Group 1 comprises pulmonary arterial hypertension (PAH). Groups 2, 3, 4, and 5 categorize PH associated with, respectively: left heart disease, lung diseases and/or hypoxemia, chronic thromboembolic disease, and various conditions with unclear and/or multifactorial mechanisms for developing PH. Pulmonary arterial hypertension differs from the other 4 groups of PH by its characteristic histopathological changes of especially the small pulmonary arteries, progressive clinical course, and need for treatment with specific PAH medication. Pulmonary arterial hypertension can occur idiopathically (iPAH) or with associated conditions such as congenital heart defects (CHD) and connective tissue disease (CTD).[1]

Clinical Perspective on p 1764

In recent decades there have been great advances in the understanding of the pathobiology of PAH in particular, resulting in the development of several new drugs.[2,3] Simultaneously, there has been growing interest in the epidemiological features of PAH. This has led to the recent publication of several reports of registry-based epidemiological data on

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PAH among adults.[4–7] In contrast, data on the prevalence and incidence of pediatric PAH are lacking. Systematic collection of pediatric data is necessary because children with PH and PAH have been reported to present with age-specific characteristics relative to the distribution of underlying conditions, presentation, outcome, and the efficacy of treatment.[8–11]

The aim of this study was to investigate the nationwide epidemiological characteristics of pediatric PH in the Netherlands during a 15-year period (1991–2005) using 2 different registries and, further, to more specifically describe the clinical course of children with different types of PAH.

Methods

Data Collection

In the Netherlands, pediatric cardiology care is centralized within 8 university medical centers. Patients suspected of having PH are seen by pediatric cardiologists at any of these centers for initial diagnostics. For the present study, we retrospectively identified pediatric patients who had been assigned a first diagnosis of PH at any of the 8 Dutch university medical centers, at the age of 0 to 17 years, from January 1991 up to January 2006. In order to identify these patients, we accessed the Pediatric Cardiology and Dutch National Hospitalization registries. Our institutional medical ethics committee waived the need for consent because of the retrospective nature of the study.

The Pediatric Cardiology registry captures the individual records of all patients seen at a pediatric cardiology department. Each pediatric cardiology department manages its own registry. Patients are assigned diagnoses using diagnostic codes defined by the Association for European Pediatric Cardiology (AEPC; http://www.aepc.org/aepc/nid/European Paediatric Cardiac Coding). To identify patients, AEPC diagnostic codes for primary and secondary PH/PAH were used (10.13.01–10.13.51, 10.15.01, 10.20.16, 15.22.31, and 15.80.22).

The Dutch National Hospitalization registry consists of records of all hospitalizations at any hospital in the Netherlands. Patients are assigned diagnoses at the time of hospital discharge. The discharge diagnostic codes are based on the International Statistical Classification of Diseases (ICD), endorsed by the World Health Organization. During the current study, the ninth revision of this classification was used (ICD-9; http://www.cdc.gov/nchs/icd.htm). In order to obtain individual record data, we accessed this database at each of the 8 university medical centers. To identify patients, ICD-9 diagnostic codes for primary and secondary PH/PAH were used (416.0, 416.8, and 416.9).

Accuracy and Assignment of Diagnoses

In order to assess the accuracy of the diagnosis of PH, 1 investigator (R.L.E.v.L.) reviewed the medical files of all identified unique patients (n=3867). Patients in whose medical files there was no diagnosis of PH (n=537), as established by the treating physician, were regarded as coding error and excluded from analysis. Overestimation of the prevalence of PAH on the basis of inexpert registries has been suggested previously, and justifies a check on the accuracy of the diagnosis when using such numbers.[6] Also, patients whose medical files were missing (n=65) were excluded. After reviewing all available data from the medical file, the investigator assigned each remaining patient to a diagnostic PH category according to the latest clinical classification of PH.[1]

In pediatrics, transient forms of PAH can be recognized, such as persistent PH of the neonate (PPHN). The clinical classification of PH categorizes PPHN as PAH.[1] However, PPHN has a natural history, treatment, and outcome that are amply different from those of other forms of PAH.[12] Importantly, in many patients with PPHN, the PAH resolves during the neonatal period. The same holds for patients with CHD and systemic-to-pulmonary shunt in whom PAH is diagnosed early before development of advanced pulmonary vascular disease (flow PAH). Flow PAH refers to a condition of increased pulmonary arterial pressure (PAP) caused by increased pulmonary blood flow (following Ohm's law) in the presence of normal or mildly elevated pulmonary vascular resistance (PVR) and normal pulmonary capillary wedge pressure. This situation is unique in that this early stage of pulmonary vascular disease is potentially reversible when the increased pulmonary blood flow is normalized by correction of the CHD. This is in contrast to patients with PAH due to CHD and (long-standing) systemic-to-pulmonary shunts in whom PAH has become progressive because of advanced pulmonary vascular disease and correction of the CHD is contraindicated (PAH-CHD).[13] In order to distinguish transient forms of PAH from progressive PAH, we assigned patients with PPHN and flow PAH to the subgroup transient PAH. All nontransient forms of PAH, including iPAH and PAH-CHD, were assigned to the subgroup "progressive PAH."

In order to further assess the accuracy of the diagnosis of progressive PAH (Group 1, n=156), we reviewed whether the diagnosis had been established by right heart catheterization (RHC) and/or echocardiography. According to the recent formal definition for diagnosing PAH, RHC is required with measurement of increased mean pulmonary arterial pressures (mPAP, ≥25 mm Hg) and normal pulmonary capillary wedge pressure (<15 mm Hg).[1,12] Reported echocardiographic criteria for estimating the presence of PH are maximal systolic tricuspid regurgitant velocity >2.8 m/s, maximal diastolic pulmonary regurgitation flow velocity >2.8 m/s, presence of right-to-left shunt, and other echocardiographic features such as ventricular septal bowing in the absence of right ventricular outflow tract obstruction.[12,14]

Right heart catheterization was performed in 111 patients with progressive PAH. Of these, 2 were still excluded because of mPAP <25 mm Hg. The remaining patients had either mPAP ≥25 mm Hg or, in 11 cases in which no mPAP was documented, a right ventricular pressure at systemic level without right ventricular outflow tract obstruction. Pulmonary venous hypertension was ruled out in all patients either by a pulmonary capillary wedge pressure, left atrial or left ventricular end-diastolic pressure <15 mm Hg, or by the absence of left ventricular dysfunction and left obstructive heart disease. In the remaining 45 patients, the diagnosis had been made solely by echocardiography. In all these cases a diagnosis of PAH was plausible on the basis of the following variables: right-to-left shunting through a heart defect (n=29), tricuspid regurgitant maximal velocity ≥2.8 m/s (n=11, mean 3.6±0.6m/s), pulmonary regurgitant maximal velocity ≥2.8 m/s (n=6, mean 3.2±0.6m/s), and/or leftward ventricular septal bowing in the absence of right ventricular outflow tract obstruction (n=18). No echocardiographic signs of left heart failure and/or pulmonary venous congestion were present in these patients. Echocardiography-confirmed patients appeared significantly younger than RHC-confirmed patients. Other patient characteristics and survival estimates did not differ between both subgroups (See results and online-only Data Supplement Table I).

Patients with PAH-CHD were categorized into 6 subgroups: (1) without shunt, (2) with pretricuspid shunt, (3) with post-tricuspid shunt, (4) accelerated, (5) with abnormal development of the pulmonary vasculature (PAH-CHD-APV), and (6) after shunt closure.

Pulmonary arterial hypertension with CHD without shunt comprised patients with CHD without previous shunt (eg, coarctation of the aorta). Pulmonary arterial hypertension with CHD with pretricuspid shunt represented patients with shunts before the level of the tricuspid valve (eg, atrial septal defects). Patients with PAH-CHD with post-tricuspid shunt (or Eisenmenger syndrome) had unrestrictive shunt defects below the level of the tricuspid shunt (eg, ventricular septal defects [VSD]).[10,15] Accelerated PAH-CHD involved infants who developed advanced PAH in the first weeks to months of life in the presence of an unrestrictive post-tricuspid shunt defect. Because this is distinct from the usual time path for the development of PAH caused by systemic-to-pulmonary shunt, we previously named this group accelerated PAH-CHD.[10] Pulmonary arterial hypertension with CHD-APV represented patients with scimitar syndrome, pulmonary atresia with VSD and major aortopulmonary collaterals, and unilateral absence of the pulmonary artery.

Table 1. Baseline Characteristics of all PH Patients

	All PH Patients (n=3263)	Transient PAH (n=2660)		PH Crisis (n=31)	Progressive PAH (n=154)	PH–Left Heart Disease (n=160)	PH–Lung Disease (n=253)	CTE-PH (n=5)	*P* Overall*
		PPHN (n=1548)	Flow PAH (n=1112)						
Age at diagnosis, y	0.0 (0–0.3)	0.0* (0.0–0.0)	0.3 (0.2–0.6)	0.7 (0.3–7.8)	2.2* (0.4–6.7)	0.8 (0.1–10.0)	0.0 (0.0–0.5)	13.6 (0.1–6.1)	<0.001
Females	1496 (46)	669 (43)	557 (50)	15 (48)	80 (52)*	69 (43)	104 (41)	2 (40)	0.003
Congenital heart defects									
Total	1681 (52)	238 (15)	1110 (99)	0	116 (75)	160 (100)	55 (22)	2 (40)	<0.01
Systemic-to-pulmonary shunt									
Pretricuspid shunt	122 (4)	14 (<1)	82 (7)		5 (3)	11 (7)	10 (4)	0	
Post-tricuspid shunt	1344 (41)	196 (13)	1027 (92)		68 (44)	11 (7)	40 (16)	2 (40)	
CHD with APV	38 (1)	0	0		38 (25)	0	0	0	
No systemic-to-pulmonary shunt	177 (5)	28 (2)	1 (<1)		5 (3)	138 (86)	5 (2)	0	
Syndromes									
Total	559 (17)	84 (5)	349 (31)	6 (19)	60 (39)	11 (7)	49 (19)	0	<0.01
Down	381 (12)	43 (3)	285 (26)	4 (13)	27 (18)	3 (2)	19 (8)	0	<0.01
Velocardiofacial	25 (<1)	4 (<1)	11 (<1)	0	10 (6)	0	0	0	. . .
Pierre-Robin	9 (<1)	0	3 (<1)	0	0	0	6 (2)	0	. . .
Noonan	7 (<1)	2 (<1)	1 (<1)	0	2 (1)	1 (<1)	1 (<1)	0	. . .
Other specific syndromes	66 (2)	24 (2)	24 (2)	0	4 (2)	2 (1)	12 (5)	0	. . .
Various chromosomal defects	19 (<1)	5 (<1)	13 (1)	0	0 (1)	0	1 (<1)	0	. . .
Metabolic diseases	7 (<1)	2 (<1)	0	1 (3)	0	3 (1)	1 (<1)	0	. . .
Undefined syndromes	45 (1)	4 (<1)	12 (1)	1 (3)	17 (11)	2 (1)	9 (4)	0	. . .

Data are presented as n (%) or median (interquartile range).

**P* indicates overall *P* value across all groups. Significant pairwise differences are discussed in the text and . . . indicates no overall statistical analysis performed because of small patient numbers in subgroups.

PH indicates pulmonary hypertension; PAH, pulmonary arterial hypertension; CTE-PH, chronic thromboembolic PH; PPHN, persistent pulmonary hypertension of the newborn; flow PAH, patients with increased pulmonary blood flow (due to congenital heart defects) and PAH in whom PAH resolves after correction of the congenital heart defect; PH crisis, transient PAH during event of respiratory tract infection; Pretricuspid shunt, atrial septal defect±abnormal pulmonary venous return±additional cardiac anomalies; Post-tricuspid shunt, complete atrioventricular septal defect±ventricular septal defect±patent ductus arteriosus±atrial septal defect±additional cardiac anomalies, truncus arteriosus, hemitruncus, aortopulmonary window, or monoventricle; CHD with APV, congenital heart defects with abnormal development of pulmonary vasculature (scimitar syndrome, pulmonary atresia VSD major aortopulmonary collaterals, and unilateral absence of pulmonary artery); No systemic-to-pulmonary shunt, coarctation of aorta, aortic stenosis, mitral valve stenosis, cor triatriatum, and left ventricular dysfunction.

Other specific syndromes include VACTERL (n=11); trisomy 18 (n=10), CHARGE (n=5); Goldenhar (n=5); Potter (n=4); Cat Eye, Cri du chat, Kartagener, Turner, and Jacobsen (n=2 of each); Rubinstein-Taybi (n=3); and trisomy 13, 1p36 deletion, Wolf-Hirschhorn, osteochondroplasia, Cornelia de Lange, Holt-Oram, Klinefelter, Marfan, Prader-Willy, oculo-facio-cardio-dental, Pallister-Killian, Short rib-polydactyly, Schwartz-Jampel, muscular dystrophy, Saethre-Chotzen, NOMID (neonatal onset multisystem inflammatory disease), prune belly, and Swyer James (n=1 of each).

Metabolic disorders include glycogen storage diseases (Pompe, n=2); peroxisomal disorders (Zellweger, rhizomelic chondrodysplasia punctata), methylcrotonyl-CoA carboxylase deficiency, mitochondrial energy metabolism defects, and cytochrome C-oxidase deficiency (n=1 of each).

Various chromosomal defects include trisomy 2, trisomy 7p, partial trisomy 8, partial trisomy 1, translocation chromosome 9 and 14; unbalanced translocation chromosome 4 and 5, unbalanced translocation chromosome 1 and 10, unbalanced translocation chromosome 1 and 9, translocation chromosome 1 and 3, translocation chromosome 14 and 21, balanced translocation 13 and 18, inversion chromosome 18, inversion chromosome 20, deletion chromosome 4, der chromosome 9, 13q deletion, 18q deletion, and 18p deletion/18q duplication.

Undefined syndromes include clinical dysmorphic features and/or psychomotor retardation without chromosomal abnormalities.

These patients were categorized separately because of the joint involvement of CHD and abnormal development of the pulmonary vasculature, which distinguishes this group from patients with CHD and normally developed pulmonary vasculature.

Pulmonary hypertension may also present with pulmonary hypertensive crises during a respiratory infection or during/after anesthesia for (surgical) procedures (PH crisis). These crises may resolve after treatment and removal of the trigger for the crisis or persist followed by death. Patients with known PH may experience such a crisis during their disease course. Also, patients not previously diagnosed with PH may present for the first time with a PH crisis. In the absence of generally accepted criteria for PH crisis, in this study its occurrence was based on the typical clinical picture of lowered systemic circulation accompanied by signs of acute right ventricular failure such as increased systemic venous pressure or increased cyanosis and increased right-to-left shunting in shunt patients. These signs may or may not have been verified with echocardiography or RHC.

General demographic variables (age, date at diagnosis, sex), and data on the presence of syndromes were collected for all PH patients. Syndromal abnormalities, including Down syndrome, have been observed to occur frequently in pediatric PAH.[10] Date of diagnosis of PH corresponded to that of confirmatory RHC or echocardiography. For patients with PAH, additional presenting characteristics were recorded: symptoms, presence and type of associated conditions for PAH (eg, CHD and its repair status), additional hemodynamic variables and World Health Organization functional class (WHOclass). Outcome variables for the PAH patients included survival status.

Statistical Analyses

To analyze differences between PH (sub)groups, 1-way ANOVA with Bonferroni posthoc testing (age) and χ^2 tests with Bonferroni posthoc testing (sex, CHD, syndromes) were performed (Table 1). To analyze differences between iPAH and PAH-CHD, *t* tests (age, hemodynamics), Mann-Whitney U tests (WHOclass), and χ^2 tests

(sex, CHD, syndromes) were performed (Table 2). Yearly incidence was calculated by dividing the number of newly diagnosed (incident) patients by the total number of children in the Netherlands in each corresponding year. These national numbers of children were obtained from the official Statistics Netherlands registry of Dutch demographics (http://www.cbs.nl). The point prevalence for PAH on the closing date of the study (January 1, 2006) was calculated from the number of incident patients between January 1991 and January 2006, excluding those who died or were lost to follow-up. Survival for all patients with PAH and for PAH subgroups is depicted using Kaplan-Meier curves from time of diagnosis. Twelve patients were lost to follow-up. These were censored at their latest follow-up time point. Cox regression was performed to study differences in survival between the different PAH (sub)groups. In order to avoid potential effects on outcome by the inclusion of patients with echocardiography-confirmed PAH, separate survival curves were calculated for RHC- and echocardiography-confirmed PAH patients. P values <0.05 were considered significant.

Results

Patients and PH Diagnoses

During the 15-year study period, a total of 3263 pediatric patients with PH (46% women) were identified (Table 1). They had the following diagnoses: transient PAH (n=2691, 82%), progressive PAH (n=154, 5%), PH crisis (n=31, 1%), PH due to left heart disease (PH-left heart disease; n=160, 5%), PH due to lung disease and/or hypoxemia (PH-lung disease/hypoxemia; n=253, 8%) and chronic thromboembolic PH (CTE-PH; n=5, <1%; Figure 1). Patients with progressive PAH were older at diagnosis than patients with other PH diagnoses ($P<0.001$; Table 1). Patients with PPHN were younger than patients with flow PH ($P<0.001$). There were more women in the progressive PAH group than in the PPHN and PH-lung disease/hypoxemia group, although the number did not reach statistical significance.

Transient PAH (Group 1)

Transient PAH included PPHN (n=1548), flow PAH (n=1112) and PH crisis (n=31; Figure 1). In the patients with flow PAH, all but 2 had CHD with systemic-to-pulmonary shunts (Table 1). The remaining 2 patients had increased cardiac output states with increased pulmonary blood flow because of arteriovenous blood vessel malformations (giant hemangioma and vein of Galen malformation). In all flow PAH patients, PAH resolved after correction of the CHD or blood vessel malformation. In 19 patients with flow PAH, the PAH disappeared after a prolonged period after correction: median 2.7 years (range 1.0–7.9). The PH-crisis patients are described after the next section.

Progressive PAH (Group 1): Associated Conditions, Presenting Characteristics, and Survival

The remaining 154 patients with PAH had progressive PAH (Figure 1). Progressive PAH included iPAH (n=36, 23%), PAH-CHD (n=111, 72%), PAH due to connective tissue disease (PAH-CTD; n=3, 2%), PAH due to HIV infection (PAH-HIV; n=1, 1%), and pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis (PVOD/PCH; n=3, 2%; Figure 1).

In iPAH (n=36), 4 patients had a small hemodynamically insignificant CHD (VSD, n=3; patent ductus arteriosus, n=1; Table 2). In 3 other patients with iPAH, PH developed and persisted directly postnatally until death (at, respectively, 3, 4.8, and 4.8 months).

The distribution of patients over the 6 PAH-CHD subgroups is depicted in Figure 1. The types of associated CHD are listed in Table 2. All 8 patients with accelerated PAH-CHD had a syndromal disorder: Down syndrome (n=5), 1p36 deletion syndrome (n=1), and undefined/unclassified syndromes (n=2). In addition, 6 of these 8 patients had concomitant obstructive breathing problems.

Patients with PAH-CHD after shunt closure underwent cardiac surgery at a median age of 0.6 years (range 0.2–7.6). In 13 of these patients, PH persisted directly after cardiac surgery (through a median of 2.7 years, range 0.6–11.6). In the remaining 4 patients, PAH developed after a median of 1.5 years (range 0.9–7.9) after correction of their CHD and persisted throughout follow-up (median 3.8, range 0.1–7.7 years).

In the patients with PVOD/PCH (n=3), diagnosis was confirmed by postmortem histopathological lung examination. In the patients with PAH-CTD (n=3), interstitial lung disease was demonstrated with thoracic computed tomography scan in 2 and chest radiography in 1 patient. One of these patients had neonatal-onset multiinflammatory disease syndrome. In the other 2 patients, there was strong clinical suspicion of CTD although blood analyses were not conclusive. The patient with PAH-HIV (n=1) had PH, echocardiographically demonstrated, while being treated for HIV infection with clinical signs of disease and high viral load.

Fifty-one percent of progressive PAH patients were females. Idiopathic PAH patients were older than PAH-CHD patients ($P<0.01$; Table 2). Most progressive PAH patients presented with symptoms, most commonly exercise-induced dyspnea. Eleven patients (7%) presented with syncope; all these patients had iPAH. The majority of patients were in WHOclass II or III. Idiopathic PAH patients presented with worse WHOclass than PAH-CHD patients ($P=0.04$; Table 2).

Hemodynamic variables from 109 patients who underwent RHC are shown in Table 3. Compared with PAH-CHD, iPAH patients had higher aortic saturation ($P=0.05$) and lower pulmonary blood flow ($P=0.02$) and tended to have higher PVR ($P=0.07$).

Follow-up from time of diagnosis ranged from 0.1 to 15 years (median 2.6 years). Median survival for all progressive PAH patients was 7.7 years (Figure 2A). Overall, survival for PAH-CHD was better than for iPAH (median 11.7 versus 2.7 years, $P=0.03$; Figure 2B). However, within PAH-CHD, the various subgroups had significantly different survival ($P<0.001$), some showing better whereas others showing worse survival than iPAH (Figure 2C). Additional survival analyses assuming that the lost-to-follow-up patients had died revealed similar results (online-only Data Supplement Figure I). All patients with PVOD/PCH and PAH-HIV died within 1.6 years from diagnosis. Two of the 3 patients with PAH-CTD died (within 6.6 years from diagnosis). In addition to diagnosis, univariate Cox regression analysis revealed higher WHO-class ($P=0.002$) and lower mixed venous saturation (hazard ratio 0.94, 95% confidence interval 0.90–0.99; $P=0.009$) to be predictive for worse survival. Patient

Table 2. Baseline Characteristics of PAH Patients

	All PAH Patients (n=154)	iPAH (n=36)	PAH-CHD (n=111)	PAH-CTD (n=3)	PAH-HIV (n=1)	PVOD/PCH (n=3)	*P** iPAH vs PAH-CHD
Age at diagnosis, y	2.2 (0.4–6.7)	4.3 (0.9–11.1)	1.4 (0.3–4.6)	7.1 (6.7–13.4)	5.8	9.0 (0.5–15.2)	<0.01
Females	80 (51)	17 (47)	61 (54)	1 (33)	0	1 (33)	0.42
WHO							
Functional class I	18 (12)	3 (8)	15 (14)	0	0	0	0.04
Functional class II	57 (39)	10 (28)	46 (44)	0	0	1 (33)	
Functional class III	56 (38)	14 (39)	38 (37)	2 (67)	1 (100)	1 (33)	
Functional class IV	16 (11)	9 (25)	5 (5)	1 (33)	0	1 (33)	
Unknown	7	0	7	0	0	0	
Presenting symptoms							
Yes	130 (89)	32 (89)	91 (82)	3 (100)	1 (100)	3 (100)	0.83
Other	17 (11)	4 (11)	13 (12)	0	0	0	
Unknown	7	0	7	0	0	0	
Dyspnea, exercise induced	108 (70)	26 (72)	75 (68)	3 (100)	1 (100)	3 (100)	
Dyspnea	66 (43)	18 (50)	42 (38)	3 (100)	1 (100)	2 (67)	
Chest pain	2 (1)	2 (6)	0	0	0	0	
Syncope	11 (7)	11 (31)	0	0	0	0	
Congenital heart defects							
Total	116 (75)	4 (11)	111 (100)	0	0	1 (33)	<0.001
Systemic-to-pulmonary shunt							
Pretricuspid shunt							
ASD±PAPVR	5 (3)	0	5 (5)			0	
Post-tricuspid shunt							
VSD±PDA±ASD	30 (19)	4 (11)	26 (23)			0	
Complex	38 (25)	0	37 (33)			1 (33)	
CHD with APV	38 (25)	0	38 (34)			0	
No systemic-to-pulmonary shunt	5 (3)	0	5 (5)			0	
Syndromes							
Total	60 (39)	11 (31)	47 (42)	1 (33)	0	1 (33)	0.21
Down	27 (18)	4 (11)	22 (20)	0		1 (33)	0.23
Velocardiofacial	10 (6)	0	10 (9)	0		0	0.054
Noonan	2 (1)	1 (3)	1 (<1)	0		0	. . .
Other specific syndromes	4 (3)	0	3 (3)	1 (33)		0	. . .
Undefined syndromes	17 (11)	6 (17)	11 (10)	0		0	0.27

Data are presented as n (%) or median (interquartile range).

P indicates pairwise differences between iPAH and PAH-CHD. Significant differences are discussed in the text and . . . indicates no overall statistical analysis performed due to small patient numbers in subgroups.

PAH indicates pulmonary arterial hypertension; iPAH, idiopathic PAH; PAH-CHD, PAH associated with congenital heart defects; PAH-CTD, PAH associated with connective tissue disease; PAH-HIV, PAH associated with HIV infection; PVOD/PCH, pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis; CHD with APV, congenital heart defects with abnormal development of pulmonary vasculature (eg, scimitar syndrome); pretricuspid shunt, atrial septal defect (ASD)±partially anomalous pulmonary venous return (PAPVR); post-tricuspid shunt, ventricular septal defect±patent ductus arteriosus (PDA)±ASD±additional cardiac anomalies and complex CHD: monoventricle (n=14), truncus arteriosus (n=1), complete atrioventricular septal defect (n=22), transposition of great arteries without VSD+aortopulmonary shunt (n=1); and CHD with APV, congenital heart defects with abnormal development of pulmonary vasculature: scimitar syndrome (n=25), pulmonary atresia+VSD+major aortopulmonary collaterals (n=12), unilateral absence of pulmonary artery (n=1); no systemic-to-pulmonary shunt, coarctation of the aorta (n=1), aortic stenosis (n=2), and transposition of great arteries without VSD neonatally corrected (n=2).

Repair status: In the pretricuspid shunt group, n=1 underwent complete surgical correction of ASD; in the post-tricuspid shunt group, n=17 underwent complete surgical correction of their CHD (of whom n=1 later developed, and was categorized as, PCH), and n=7 underwent palliative procedures (closure of perimembranous VSD, multiple muscular VSDs still open n=1; closure of ASD and VSD, PDA still open n=1; monoventricle: aortopulmonary shunt n=3, inadequate banding of pulmonary artery n=2); In CHD with APV: n=17 underwent palliative procedures (aortopulmonary shunts n=6, [partial] unifocalisations n=6, [partial] closure of aortopulmonary collaterals n=5).

Other specific syndromes: Jacobsen, NOMID (neonatal onset multisystem inflammatory disease), 1p36 deletion, and Wolf Hirschhorn (4p deletion). Undefined syndromes: clinical dysmorphic features and/or psychomotor retardation without chromosomal abnormalities.

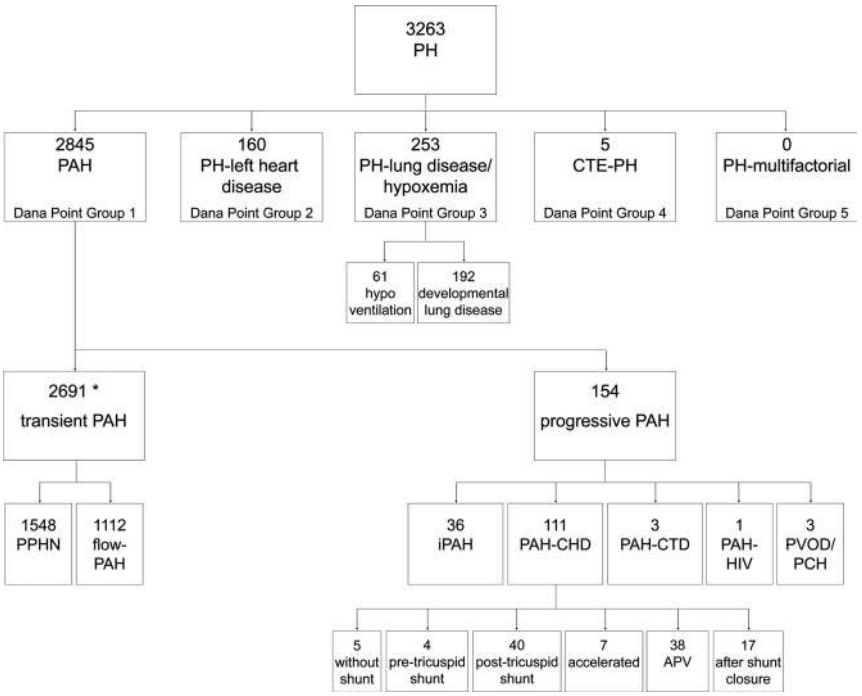

Figure 1. Diagnoses of all children with pulmonary hypertension. PH indicates pulmonary hypertension; PAH, pulmonary arterial hypertension; CTE, chronic thromboembolic; PPHN, persistent pulmonary hypertension of the newborn; flow-PAH, patients with increased pulmonary blood flow (due to CHD) and PAH in whom PAH resolves after correction of the congenital heart defect; iPAH, idiopathic pulmonary arterial hypertension; PAH-CHD, PAH associated with CHD; PAH-CTD, PAH associated with connective tissue disease; PAH-HIV, PAH associated with HIV infection; PVOD/PCH, pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis; and APV, CHD associated with abnormal development of pulmonary vasculature (eg, scimitar syndrome). *Includes PH crisis, transient PAH during event of respiratory tract infection (n=31).

characteristics did not differ between the RHC- and echocardiography-confirmed PAH patients. (Figure 3, online-only Data Supplement Table I).

Pulmonary arterial hypertension—targeted drugs were prescribed over the years in increasing numbers, most from 2001 onwards, reflecting evolving treatment guidelines: calcium channel blockers from 1992 (n=16), epoprostenol from 1996 (n=16), beraprost in 2003 (n=1), bosentan from 2001 (n=31), and sildenafil from 2004 (n=9). Pulmonary arterial hypertension drugs were prescribed to 53 of all progressive

Table 3. Baseline Hemodynamic and Echocardiographic Characteristics of Patients With iPAH and PAH-CHD

	All PAH Patients (n=154)	iPAH (n=36)	PAH-CHD (n=111)	*P*
Diagnosis of pulmonary hypertension				
Cardiac catheterisation	109 (71)	30 (83)	74 (67)	
Echocardiography	45 (29)	6 (17)	37 (33)	
Hemodynamics				
Aortic saturation, %	93±8	95±8	91±8	0.05
Mixed venous saturation, %	62±10	62±11	63±9	0.84
Mean right atrial pressure, mm Hg	7±3	6±4	7±3	0.42
Mean pulmonary arterial pressure, mm Hg	51±20	56±20	49±19	0.08
Mean pulmonary capillary wedge pressure, mm Hg	9±5	8±3	9±4	0.17
Mean systemic arterial pressure, mm Hg	64±18	67±17	59±18	0.12
mPAP/mSAP	0.9±0.3	0.8±0.3	0.9±0.2	0.21
Pulmonary blood flow indexed, $L \cdot min^{-1} \cdot m^{-2}$	3.1±1.5	2.6±0.8	3.5±1.8	0.02
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.7±0.7	2.7±0.7	2.7±0.8	0.98
Qp/Qs	1.2±0.8	1.0±0.1	1.3±1.1	0.08
Pulmonary vascular resistance index, $WU \cdot m^2$	17.8±12.7	21.4±12.7	15.4±10.6	0.07
Systemic vascular resistance index, $WU \cdot m^2$	20.9±10.0	23.0±10.1	19.2±9.7	0.22
PVR/SVR	1.1±0.9	0.9±0.5	1.2±1.1	0.40
Echocardiography				
Maximal systolic tricuspid regurgitant velocity	3.9±0.7	4.0±1.2	3.6±0.6	0.80
Maximal diastolic pulmonary regurgitant velocity	3.2±0.6	3.2±0.4	3.2±0.6	0.22

Data are presented as n (%) and mean±SD. iPAH indicates idiopathic pulmonary arterial hypertension; PAH-CHD, PAH associated with congenital heart defects; mPAP/mSAP, mean pulmonary to systemic arterial pressure ratio; Qp/Qs, pulmonary to systemic blood flow ratio; PVR/SVR, pulmonary to systemic vascular resistance ratio; and WU, Woods units.

P values are for iPAH vs PAH-CHD.

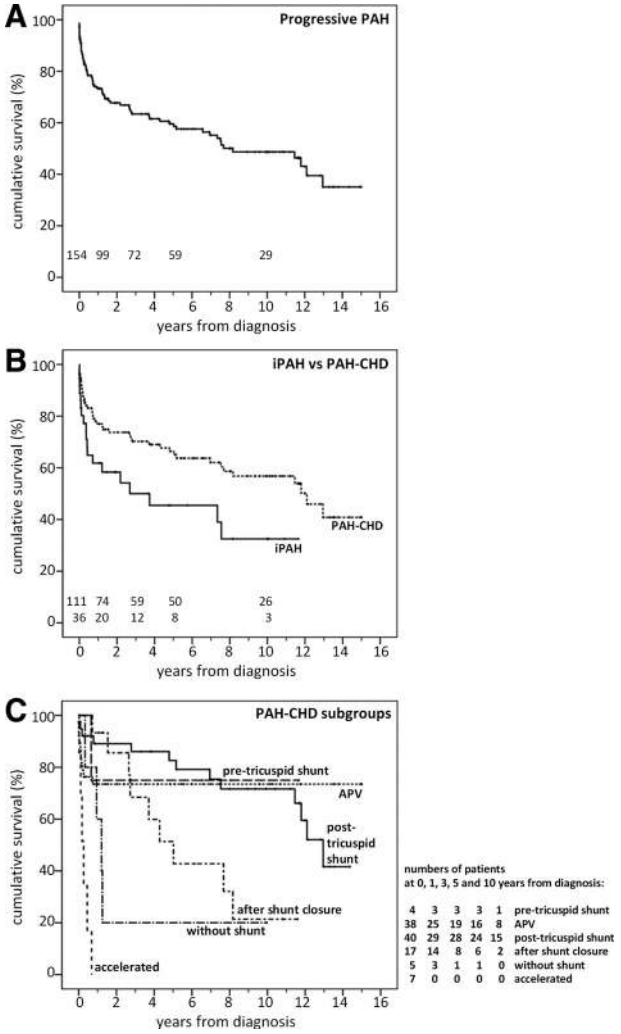

Figure 2. Survival for progressive pulmonary arterial hypertension in children **A**, Survival for all patients with progressive PAH; 1, 3, and 5-year survival: 73%, 63%, and 60%, respectively. **B**, Survival stratified for iPAH and PAH-CHD; 1, 3, and 5-year survival: iPAH versus PAH-CHD: 62%, 50%, and 46% versus 77%, 70%, and 66%, respectively ($P=0.03$). **C**, Survival for all subgroups of PAH-CHD; 1, 3, and 5-year survival: pretricuspid shunt (75%, 75%, and 75%), APV (74%, 74%, and 74%), post-tricuspid shunt (89%, 86%, and 83%), after shunt closure (93%, 68%, and 51%), without shunt (60%, 20%, and 20%), and accelerated (0%, 0%, and 0%), respectively. PAH indicates pulmonary arterial hypertension; iPAH, idiopathic pulmonary arterial hypertension; PAH-CHD, PAH associated with congenital heart defects; and APV, abnormal development of the pulmonary vasculature. See text for explanation of PAH-CHD subgroups. Overall difference in survival: $P<0.001$; accelerated PAH-CHD ($P<0.01$) and PAH-CHD without shunt ($P=$NS) had worse survival than iPAH. In contrast, PAH-CHD with post-tricuspid shunt ($P<0.01$) and PAH-CHD-APV ($P=0.03$) had better survival than iPAH. Pulmonary arterial hypertension with CHD with pretricuspid shunt ($P=$NS) and PAH-CHD after shunt closure showed similar survival to iPAH ($P=$NS).

PAH patients (34%): 25 of iPAH (69%), and 26 of PAH-CHD patients (23%). Thirty-seven patients received 1 drug, 12 patients 2 drugs, and 4 patients received 3 different drugs.

PH Crisis

Pulmonary hypertension crisis occurred in 194 flow PAH patients (17%): perioperatively (n=171) or during respiratory

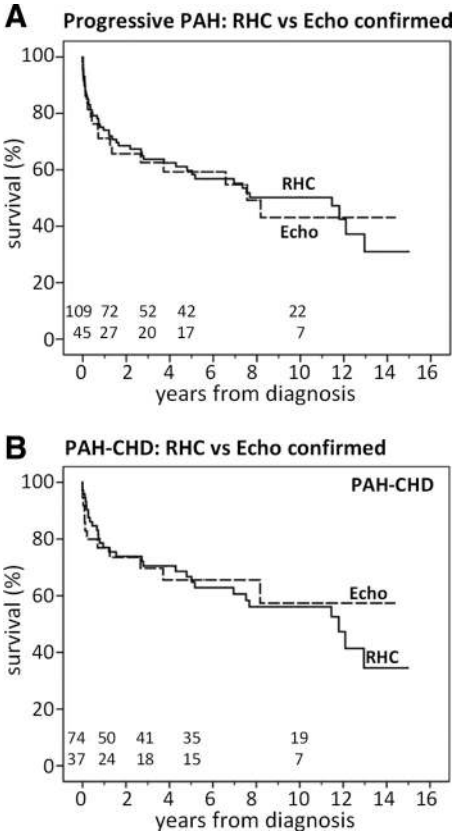

Figure 3. Survival for progressive PAH in children, separately for RHC and echocardiography-confirmed patients. **A**, Survival for RHC- versus echocardiography-confirmed patients with progressive PAH: 1-, 3-, and 5-year survival, RHC- versus echocardiography-confirmed patients: 74%, 64%, and 60% versus 71%, 63%, and 59%, respectively. **B**, Survival for RHC-confirmed versus echocardiography-confirmed patients with PAH-CHD; 1-, 3-, and 5-year survival RHC- versus echocardiography-confirmed patients: 77%, 71%, and 67% versus 77%, 70%, and 66%, respectively ($P=$NS). PAH indicates pulmonary arterial hypertension; RHC, right heart catheterization; Echo, echocardiography; and PAH-CHD, PAH associated with congenital heart defects.

tract infections (n=23). Pulmonary hypertension crises were reported in 21 of 154 progressive PAH patients (14%): perioperatively (n=7) or during respiratory tract infections (n=14), and more frequently in iPAH (9 of 36, 25%) than in PAH-CHD (12 of 111, 11%, Pearson χ^2, $P=0.04$). However, PH crisis also manifested itself during respiratory tract infections in 31 patients without a previous or post diagnosis of PH (Figure 1). Six of these patients (19%) had a syndromal abnormality.

PH Diagnoses (Groups 2–5)

Patients with PH-left heart disease (n=160, Figure 1) had various left-sided CHD causing increased pulmonary venous pressures and PH (Table 1). Patients with PH-lung disease/hypoxemia (n=253,Figure 1) had: obstructive upper airway breathing disorders (n=61) caused by small upper airways, laryngo-tracheomalacia, micrognathia and/or enlarged adenoid/tonsils/tongue, and pulmonary developmental disorders associated with lung hypoplasia (n=192). The latter included chronic lung disease of prematurity (n=60), congenital diaphragmatic hernia (n=123), and rare congenital pulmonary

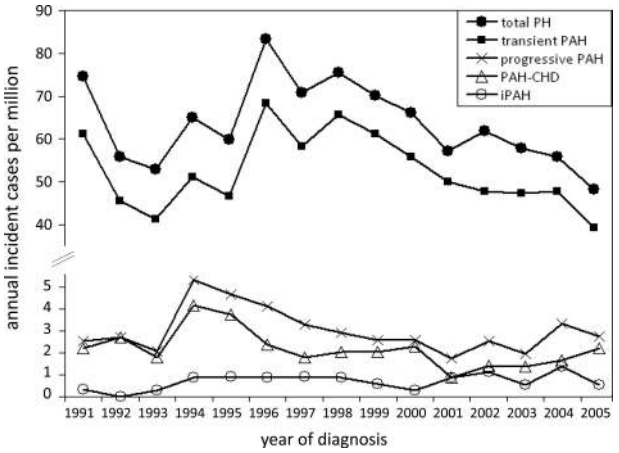

Figure 4. Annual incidence rates for pediatric pulmonary hypertension. PH indicates pulmonary hypertension; PAH, pulmonary arterial hypertension; PAH-CHD, PAH associated with congenital heart defects; and iPAH, idiopathic PAH.

disorders (n=9, adenomatoid malformation of the lung and pulmonary lymphangiectasia).

CTE-PH (n=5, Figure 1) included 1 patient with chronic thromboembolic disease and thrombi located distally in the pulmonary arteries. The remaining 4 patients had thrombi located proximally in the pulmonary arteries. Two of these latter patients had chronic thrombi and 2 had an acute pulmonary thromboembolic event.

Incidence and Prevalence

Yearly incidence rates for all PH diagnoses averaged 63.7 cases per million children (Figure 4). The highest rates were seen for transient PAH: 30.1 and 21.9 cases per million children for, respectively, PPHN and flow PAH. For progressive PAH, annual incidence rates averaged 3.0 cases per million children. For iPAH and PAH-CHD, these rates were respectively 0.7 and 2.2 cases per million.

Excluding 68 deaths and 12 patients who were lost to follow-up, 74 of the 154 incident progressive PAH patients were alive on January 1st2006. Therefore, the point prevalence for progressive PAH in the Dutch pediatric population (3.643 million) was 20 cases per million. The point prevalence for PAH-CHD and iPAH was, respectively, 15.6 and 4.4 cases per million children.

Syndromal Abnormalities and Genetic Defects

Various syndromes or syndromal abnormalities were present in 17% of all PH patients (Table 1). These were observed especially in progressive PAH (39%; $P<0.01$; Table 1). Within the progressive PAH subgroups, the highest percentage of syndromes were seen in PAH-CHD (42%; $P=0.21$; Table 2). Down syndrome was by far the most common (12% of all PH patients, 18% of progressive PAH). Undefined syndromes (1% of all PH patients) comprised patients with clinical dysmorphic features and/or psychomotor retardation without defined chromosomal abnormalities. Interestingly, most of these undefined syndromes were seen in patients with progressive PAH (11%; Table 1), and, more specifically, in iPAH (17%; $P=0.27$; Table 2).

Screening for BMPR2 (bone morphogenetic protein receptor type 2) gene mutations was performed in 19 patients with iPAH. BMPR2 gene mutations were found in 4 patients: 2 with familial PAH and 2 with sporadic PAH.

Discussion

This study describes the epidemiological features of pediatric PH, derived from nationwide data encompassing a 15-year period. Over 80% of all pediatric PH were transient forms of PAH. Progressive PAH accounted for 5% of all patients, with PAH-CHD and iPAH representing the most common subgroups. Pulmonary arterial hypertension with CHD constituted a heterogeneous group of patients. Concomitant syndromes were common. This study is the first to report incidence and prevalence rates for pediatric PH and shows that these rates were higher for PAH-CHD than for iPAH. Overall, survival for PAH-CHD was better than for iPAH. However, specific PAH-CHD subgroups showed worse or similar survival compared with iPAH.

This series confirms a different distribution of pediatric progressive PAH diagnoses compared with that observed in adults, in whom PAH-CTD occurs more frequently.[4,6,7] Furthermore, the distribution of pediatric PH diagnoses appears to be age specific, consisting of various diagnoses not seen in adults. Importantly, discrimination of patients with transient forms of PAH is imperative because their clinical course, treatment, and prognosis differ significantly from that of progressive PAH. Obviously, patients with flow PAH should not be treated with current anti-PAH drugs, but need correction of their CHD to prevent evolution to progressive PAH. These data underscore that, although abandoned in the recent Dana Point diagnostic classification of pulmonary hypertension, PVR is mandatory as a criterion for progressive PAH in children, primarily because of the significant number of patients with congenital heart disease. The authors therefore advocate that the definition of progressive PAH in children (ie, pediatric pulmonary hypertensive vascular disease) should include, in addition to mPAP $\geq$25 mm Hg and PCWP $\geq$15 mm Hg, indexed PVR $\geq$3 Woods Units.m2

Historically, incidence rates for iPAH were estimated to be 1 to 2 cases per million adults.[16] Recently, larger epidemiological registries in adults estimated similar annual incidence rates for iPAH, ranging from 1 to 3.3, and prevalence rates ranging from 5.9 to 25 cases per million.[4,6] We observed lower incidence and prevalence rates for pediatric iPAH (respectively, 0.7 and 4.4 cases per million). In contrast, we observed higher incidence and prevalence rates for pediatric PAH-CHD (respectively, 2.2 and 15.6 cases per million) than those reported in adults (respectively, 0.4–2.2 and 1.7–12 per million adults).[4,6] These latter reports, mainly based on PAH referral registries, acknowledge a low representation of PAH-CHD in adults because of their incomplete referral to specialized PAH centers. The current study avoided potential referral biases by identifying patients on a nationwide basis via both general pediatric cardiology and general hospital registries.

Pulmonary arterial hypertension with CHD in childhood points to various heart defects with specific hemodynamic profiles associated with different temporal evolution patterns of pulmonary vascular disease or with congenital maldevel-

opment of the pulmonary vasculature. This heterogeneity of PAH-CHD is being recognized increasingly. Unfortunately, the latest clinical classification of PH, updated by the inclusion of 4 clinical classes within PAH-CHD, does not yet suffice for categorizing the pediatric age-group specific presentations of PAH-CHD, illustrated by the group of accelerated PAH-CHD and CHD with abnormal development of pulmonary vasculature.[1,15]

Adults with Eisenmenger syndrome are reported to have better survival than those with iPAH.[17–19] However, it is important to realize that such studies suffer from selection bias because most exclude patients who died during childhood. In this study, pediatric survival rates in PAH-CHD were worse than those reported in adults (median survival 11.4 years in our study versus 30–40 years in adults).

Survival for pediatric PAH-CHD after shunt closure was at least as bad as that in iPAH. This observation corroborates previous reports[20] and validates concerns about repairing CHD in patients with advanced PAH because their outcome may be worse with corrected than with uncorrected shunt. In the Netherlands, where a well-developed national preventive child health service is in place, we found that 1.5% of all pediatric patients with CHD and flow-associated PAH showed persistence or new development of PAH after closure of the shunt. Previously in adults, higher proportions of patients with PAH persisting or developing after closure of CHD have been reported (3% to 13%).[21,22]

The development of advanced PAH in CHD generally requires long-standing increased pulmonary blood flow with or without increased pulmonary pressures.[15] We describe a subgroup of infants with CHD with post-tricuspid shunt who showed accelerated development of PAH in the weeks to months after birth and whose survival was worse than that of infants with iPAH. This suggests additional factors in the pathogenesis of PAH, such as disturbed postnatal adaptation of the pulmonary vascular bed or increased susceptibility for development of PAH. Interestingly, all the patients with accelerated PAH-CHD had syndromal abnormalities, including Down syndrome, which has been thought to be associated with higher susceptibility for PAH.[23] Detailed documentation of these clinical associations in combination with expanding genetic analysis techniques may allow identification of novel molecular pathways involved in the development of PAH.

Half of the children with progressive PAH presented with WHOclass I or II, and the overall hemodynamic profile was characterized by normal filling pressures and maintained cardiac index despite severely elevated mPAP and PVR. Therefore, a relatively favorable clinical presentation in the presence of severe pulmonary vascular disease may be misleading and should not justify delay of medical treatment.

We demonstrated that in the past 2 decades in a country with general access to high-quality standard of care, only 71% of the children diagnosed with progressive PAH fulfilled the diagnostic criteria according to the official current guidelines. These guidelines require RHC for confirmation of the diagnosis of PAH. Currently, children suspected of PAH in the Netherlands are referred to 1 referral center. This national organization of care concentrates clinical expertise and guarantees up-to-date care for children with this rare but devastating disease.

The present study is limited by its retrospective character. The registries used to identify patients with PH were not specifically designed to characterize the type of PH according to the current clinical classification, and no uniform criteria for assigning PH codes were predefined. In order to improve the accuracy of PH diagnosis as adequately as possible in this retrospective context, we reviewed the medical files of each identified patient looking for evidence for the presence and type of PH and excluded patients (almost 15% of all) with no evidence of PH. This finding supports previously suggested overestimation of PAH on the basis of nonexpert registries.[6] A medical file was missing in 65 patients coded as having PH. This number, however, could potentially result in only a minimal underestimation of the reported incidence and prevalence rates. In contrast to current clinical guidelines, a confirmative RHC was not required for enrollment in this study, which might have introduced the risk of inaccurate PH diagnosis and an overestimation of PAH incidence. If none of the cases without a RHC were diagnosed with PAH, our incidence estimate for progressive PAH would decrease from 3.0 to 2.2 cases per million children. In the patients with progressive PAH, the main focus of this study, this risk was minimized by meticulous review of the medical files. Comparative analyses between RHC- and echocardiography-confirmed groups, revealing similar patient characteristics and outcome in both groups, support the notion that this risk was minimized. Importantly, the absence of the RHC requirement reduced the risk of selection bias and left truncation, which is pivotal in an epidemiological study. Nevertheless, as is inevitable in every epidemiological study, patients with unrecognized PH will have been missed.

In conclusion, this nationwide epidemiological study demonstrates that pediatric PH is characterized by age-specific diagnoses, the majority of which are transient forms of PAH. Progressive PAH is rare and associated with CHD in almost 75% of the cases. Compared to adults, incidence and prevalence rates for pediatric PAH-CHD are higher. In contrast, these rates for pediatric iPAH are lower. Pediatric PAH-CHD occurs in a heterogeneous group of patients with various presentations and disease courses. Survival of children with Eisenmenger syndrome appears to be worse than that reported in adults. The age-specific presentations of children with PAH warrants specialized diagnosis and treatment, which can be offered by specialized pediatric PAH referral centers.

Disclosures

Dr Berger has served on the speakers' bureau for Actelion and Schering. He has served as a consultant or on an advisory board for Actelion, G.S.K., and Lilly. The other authors report no conflicts.

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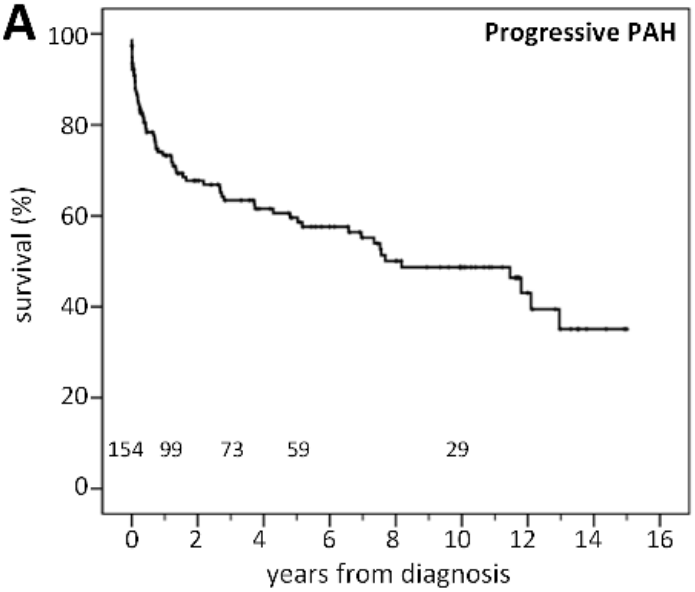
CLINICAL PERSPECTIVE

In recent years, significant progress has been achieved in understanding the epidemiology and diagnosis of pulmonary hypertension (PH) in adults. In contrast, PH in children remains poorly understood because of a lack of epidemiological and clinical data. This study portrays epidemiological features, including incidence and prevalence, of pediatric PH and especially pulmonary arterial hypertension (PAH) based on nationwide data derived from 2 general medical registries (pediatric cardiology, national hospitalization) in the Netherlands during a 15-year period. This study demonstrates that pediatric PH is characterized by several age-specific diagnoses. Over 80% of these are transient forms of PAH not seen in adults. Progressive PAH in children includes idiopathic PAH (23%) but is mainly associated with congenital heart defects (PAH-CHD; 72%). Annual incidence for all PH diagnoses was 63.7 cases per million children. For iPAH and PAH-CHD, annual incidence and point prevalence averaged 0.7 and 4.4 (iPAH), and 2.2 and 15.6 (PAH-CHD) cases per million children. Incidence of pediatric iPAH was lower than reported in adults whereas incidence of pediatric PAH-CHD was higher. The group with pediatric PAH-CHD was more heterogeneous with highly variable clinical courses. Survival of Eisenmenger syndrome in children appeared to be worse than that reported in adults. Concomitant syndromes were frequent, especially in progressive PAH (39%). Notably, in the 15-year study period, only 71% of children with a diagnosis of PAH had confirmatory right heart catheterization as required by current guidelines, emphasizing the need for increasing specific clinical expertise. This can be reached by concentrating the care for pediatric PAH in specialized centers.

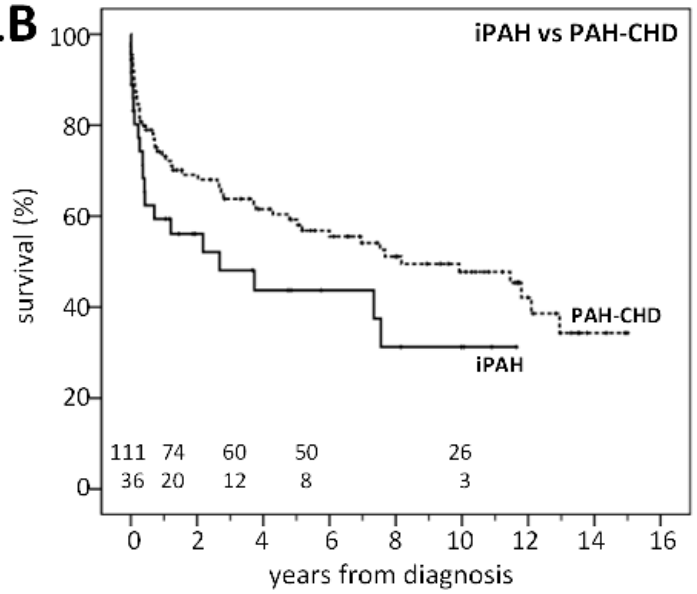
Table S1. Baseline characteristics of RHC-confirmed versus Echo-confirmed progressive PAH patients

		all progressive PAH patients n=154		RHC-confirmed n=109		Echo-confirmed n=45		p-value
		N	%	N	%	N	%	
Diagnosis	iPAH	36	23	30	27.5	6	14	0.056
	PAH-CHD	111	72	74	67.9	37	82	
	PAH-CTD	3	2	2	1.8	1	2	
	PAH-HIV	1	1	0	.0	1	2	
	PCH/PVOD	3	2	3	2.8	0	0	
CHD	Pre-tricuspid shunt	5	4	5	6	0	0	
	VSD ± PDA ± ASD	30	26	21	27	9	24	
	Complex	38	33	28	34	10	27	
	CHD with APV	38	33	21	28	17	46	
	No systemic-to-pulmonary shunt	5	4	4	5	1	3	
Age	(years, median)	2.2		3.1		.6		0.001
Sex	Male	74	48	51	47	23	51	0.625
	Female	80	52	58	53	22	49	
WHOclass	class I	18	12	11	10	7	18	0.290
	class II	57	39	43	40	14	36	
	class III	56	38	40	37	16	41	
	class IV	16	11	14	13	2	5	

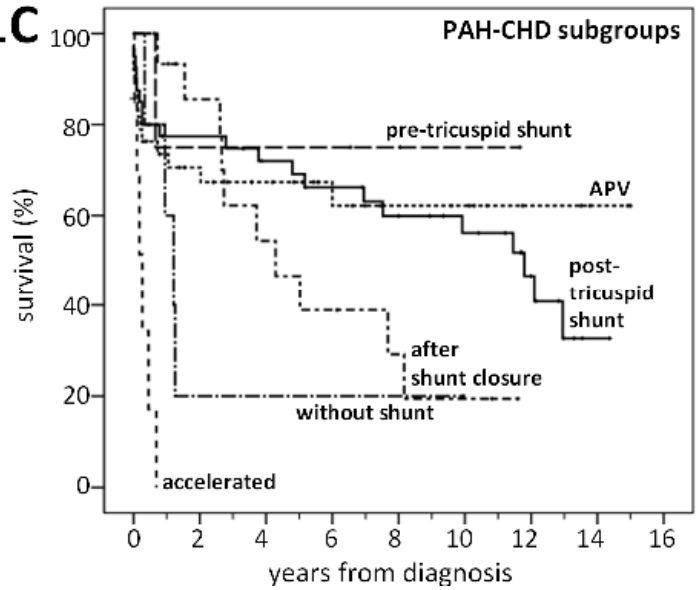
S1A



S1B



S1C



numbers of patients at 0, 1, 3, 5 and 10 years from diagnosis:

4	3	3	3	1	pre-tricuspid shunt
38	25	19	16	8	APV
40	29	28	24	15	post-tricuspid shunt
17	14	8	6	2	after shunt closure
5	3	1	1	0	without shunt
7	0	0	0	0	accelerated

Figure S1. Survival for progressive pulmonary arterial hypertension in children, 12 lost to follow-up patients assumed dead

S1A. Survival for all patients with progressive PAH;

Worst case 1, 3 and 5-year survival: 70%, 58% and 54%, respectively

S1B. Survival stratified for iPAH and PAH-CHD;

Worst case 1, 3 and 5-year survival: iPAH vs PAH-CHD: 59%, 48% and 44% vs 73%, 64% and 59%, respectively (p=0.075);

S1C. Survival for all subgroups of PAH-CHD;

Worst case 1, 3 and 5-year survival: pre-tricuspid shunt (75%, 75% and 75%), APV (74%, 67% and 67%), post-tricuspid shunt (78%, 75% and 69%), after shunt closure (93%, 62% and 47%), without shunt (60%, 20% and 20%), accelerated (0%, 0% and 0%), respectively.

Overall difference in survival: P<0.001;

iPAH vs. PAH-CHD with pre-tricuspid shunt (p=NS), vs. post-tricuspid shunt (p<0.01), vs. APV (p=0.03), vs. after shunt closure (p=NS), vs. without shunt (p=NS), vs. accelerated PAH-CHD (p<0.01).

Accelerated PAH-CHD (p<0.01) and PAH-CHD without shunt (p=NS) had worse survival than iPAH. In contrast, PAH-CHD with post-tricuspid shunt (p<0.01) and PAH-CHD-APV (p=0.03) had better survival than iPAH. PAH-CHD with pre-tricuspid shunt (p=NS) and PAH-CHD after shunt closure showed similar survival to iPAH (p=NS).