Published in final edited form as:
Lancet. 2012 February 11; 379(9815): 537–546. doi:10.1016/S0140-6736(11)61621-8.

Clinical features of paediatric pulmonary hypertension: a registry study

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See **Online** for webappendix

Contributors

RMFB, RJB, MB, TH, IS-N, and GER contributed to the conception and design of the study, obtained funding, and did the analysis and interpretation, and worked with Quanticate UK on the statistical analysis. RMFB, RJB, MB, TH, IS-N, DDI, DB, and Z-CJ contributed to data gathering. RMFB and RJB wrote the article, and RMFB, RJB, MB, TH, IS-N, GER, DDI, DB, and Z-CJ contributed to the critical revision of the report. All authors approved the final version of the report. RMFB had overall responsibility for the report.

Conflicts of interest

All authors or their institutions have received travel costs to visit executive board or investigator meetings related to the TOPP-registry from the Association for Pediatric Pulmonary Hypertension. GR has been a consultant for the Association for Pediatric Pulmonary Hypertension. RMFB has been a consultant for Actelion Pharmaceuticals, GlaxoSmithKline, Novartis, and United Therapeutics; his institution has received or has grants pending from Actelion Pharmaceuticals and Pfizer; and has received lecture fees from Actelion Pharmaceuticals. MB has been a consultant and board member for Actelion Pharmaceuticals, Pfizer, Bayer, Novartis, Eli Lilly, and GlaxoSmithKline; has received grants from Bayer and lecture fees from Actelion Pharmaceuticals, Pfizer, and Bayer; and has developed educational material for Actelion Pharmaceuticals. GER has been a consultant for Bayer, Bristol-Myers Squibb, Johnson & Johnson, Pfizer, Actelion Pharmaceuticals, Daiichi-Sankyo, Sanofi-Aventis, Boehringer Ingelheim, GlaxoSmithKline, and Takeda R&D; and has received writer's fees from Bristol-Myers Squibb, Daiichy Sankyo, Bayer, and Sanofi-Aventis. DDI has been a consultant for Actelion Pharmaceuticals, Gilead, United Therapeutics, and Pfizer; and has received grants from Gilead and developed educational material for United Therapeutics. ZCJ has been a consultant and board member for Pfizer, GlaxoSmithKline, Actelion Pharmaceuticals, United Therapeutics, and Bayer; has received grants from Actelion Pharmaceuticals, Bayer, Pfizer, and United Therapeutics; and has received lecture fees from Actelion Pharmaceuticals and Bayer. RJB has been a consultant for Actelion Pharmaceuticals, Eli Lilly, GlaxoSmithKline, Gilead, Merck, Novartis, Bayer, and Pfizer. TH, IS-N, and DB declare that they have no conflicts of interests.

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Summary

Background—Paediatric pulmonary hypertension, is an important cause of morbidity and mortality, and is insufficiently characterised in children. The Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry is a global, prospective study designed to provide information about demographics, treatment, and outcomes in paediatric pulmonary hypertension.

Methods—Consecutive patients aged 18 years or younger at diagnosis with pulmonary hypertension and increased pulmonary vascular resistance were enrolled in TOPP at 31 centres in 19 countries from Jan 31, 2008, to Feb 15, 2010. Patient and disease characteristics, including age at diagnosis and at enrolment, sex, ethnicity, presenting symptoms, pulmonary hypertension classification, comorbid disorders, medical and family history, haemodynamic indices, and functional class were recorded. Follow-up was decided by the patients' physicians according to the individual's health-care needs.

Findings—362 of 456 consecutive patients had confirmed pulmonary hypertension (defined as mean pulmonary artery pressure ≥25 mm Hg, pulmonary capillary wedge pressure ≤12 mm Hg, and pulmonary vascular resistance index ≥3 WU/m^{32}). 317 (88%) patients had pulmonary arterial hypertension (PAH), which was idiopathic [IPAH] or familial [FPAH] in 182 (57%), and associated with other disorders in 135 (43%), of which 115 (85%) cases were associated with congenital heart disease. 42 patients (12%) had pulmonary hypertension associated with respiratory disease or hypoxaemia, with bronchopulmonary dysplasia most frequent. Finally, only three patients had either chronic thromboembolic pulmonary hypertension or miscellaneous causes of pulmonary hypertension. Chromosomal anomalies, mainly trisomy 21, were reported in 47 (13%) of patients with confirmed disease. Median age at diagnosis was 7 years (IQR 3–12); 59% (268 of 456) were female. Although dyspnoea and fatigue were the most frequent symptoms, syncope occurred in 31% (57 of 182) of patients with IPAH or FPAH and in 18% (eight of 45) of those with repaired congenital heart disease; no children with unrepaired congenital systemic-to-pulmonary shunts had syncope. Despite severe pulmonary hypertension, functional class was I or II in 230 of 362 (64%) patients, which is consistent with preserved right-heart function.

Interpretation—TOPP identifies important clinical features specific to the care of paediatric pulmonary hypertension, which draw attention to the need for paediatric data rather than extrapolation from adult studies.

Funding—Actelion Pharmaceuticals.

Introduction

Pulmonary hypertension with increased pulmonary vascular resistance is associated with substantial morbidity and mortality. The most recent clinical classification defines five pulmonary hypertension groups, with pulmonary arterial hypertension (PAH) being group 1 (the full classification is provided in the webappendix).[1] PAH can be idiopathic (IPAH), heritable (HPAH), or associated with conditions (APAH) such as congenital heart disease and can present at any age. It is a rare disease with incidence and prevalence estimates of 2–3 per million and 25–50 per million, respectively.

Without treatment, median survival after diagnosis of IPAH or HPAH has been reported as 2·8 years in adults, but survival in children might be worse.[2] Clinical trials and registries have led to substantial progress in treatment of this disorder in adults.[2–6] Although pathobiology and clinical features share similarities in children and adults, paediatric pulmonary hypertension could well differ from adult disease.[7–9] Adult studies alone cannot provide a basis for optimum care for children. However, paediatric pulmonary hypertension is insufficiently characterised. The Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry is a global, prospective, observational study designed to provide information about demographics, course, treatment, and outcomes in paediatric pulmonary hypertension.[10]

Methods

Study design

TOPP is a centre-based, comprehensive registry, which was initiated on Jan 31, 2008. Enrolled patients undergo assessment, treatment, and follow-up according to the judgment of their physicians. No specific therapy or follow-up protocols are part of TOPP. Patients in clinical trials are eligible. Patients were enrolled from 31 centres in 19 countries in five continents (sites and investigators are listed at the end of the report). Patients with pulmonary hypertension caused by left-heart disease (group 2) were excluded unless the left-heart disease had been corrected and the patient had persistent pulmonary hypertension with increased pulmonary vascular resistance at least a year post-repair and no residual left-sided disease.

The study was designed and supervised by the Executive Board of the Association for Pediatric Pulmonary Hypertension (Board members are listed at the end of the report). Data management and analyses were done by a contract organisation working with the Executive Board.

Study population

We prespecified diagnosis on or after Jan 1, 2001, to provide a population representative of present practice. To minimise selection bias, physicians at all sites screened all consecutive patients presenting with suspected or confirmed PAH or pulmonary hypertension groups 3–5 (classified according to the 2003 3rd World Pulmonary Hypertension Symposium[11]) with increased pulmonary vascular resistance. Patients aged between 3 months and 18 years at the time of diagnosis with PAH (group 1), pulmonary hypertension associated with respiratory disorders (group 3), chronic thromboembolic pulmonary hypertension (group 4), or miscellaneous causes of pulmonary hypertension (group 5) were eligible if they met the prespecified haemodynamic enrolment criteria: pulmonary hypertension, increased pulmonary vascular resistance, and normal left-sided filling pressures irrespective of pulmonary hypertension group.[11] We included both newly diagnosed patients (incident; diagnosis within 3 months of enrolment) and previously diagnosed patients (prevalent; diagnosis more than 3 months before enrolment).

According to the 2003 classification,[11] cases with familial aggregation of the disease were classified as familial PAH (FPAH), although the most recent classification would use HPAH.[1] Patients with congenital heart disease with left-sided obstruction and persistent pulmonary hypertension at least a year post repair (without residual obstruction—ie, mean pulmonary capillary wedge pressure [mPCWP] ≤12 mm Hg at ≥1 year post repair with right-heart catheterisation) were also eligible (included in group 1). We did not include pulmonary venous hypertension irrespective of pulmonary vascular resistance index (PVRi, classically defined group 2) because therapy for these patients is initially directed towards treating the left-sided heart disease. Patients with APAH associated with congenital heart disease were classified as having an open, clinically significant congenital systemic-to-pulmonary shunt (unrepaired or repaired but with a substantial residual shunt), a corrected (closed) congenital systemic-to-pulmonary shunt, or as congenital heart disease that had never been associated with a congenital systemic-to-pulmonary shunt.

The diagnosis of confirmed pulmonary hypertension required right-heart catheterisation with mean pulmonary arterial pressure (mPAP) 25 mm Hg or more, PVRi 3 WU/m^{-2} or more, and mPCWP 12 mm Hg or less. In cases in which right-heart catheterisation could not be done for specific clinical reasons (eg, patient died before scheduled procedure), patients could be considered for enrolment on the basis of confirmatory echocardiography or histopathology, or both, provided that the executive board, masked to site, validated the diagnosis and agreed with why the right-heart catheterisation was not done. All patients who met enrolment criteria were informed of the registry and were eligible to provide written informed consent to participate. Parental consent was obtained for patients younger than 18 years The protocol was approved by institutional review boards and ethics committees.

Patient follow-up and data collection

We obtained patient and disease characteristics, including age at diagnosis and at enrolment, sex, ethnicity, presenting symptoms, pulmonary hypertension classification, comorbid disorders, medical and family history, haemodynamic indices, and functional class with an electronic case record form. Follow-up was decided by the patients' physicians according to the individual's health-care needs. No visits were required, but consistent with standard practice, physicians were encouraged to schedule follow-up at least yearly. All patients will be followed up for at least 3 years.

Statistical methods and analysis

TOPP was designed to enrol about 450 patients. A priori, we decided that the sample population would include incident and prevalent patients. To ensure enrolment of a sufficient number of incident cases, a 2 to 1 ratio of prevalent to incident patients was prespecified with the ability to stop enrolment of prevalent patients once the two-thirds target was reached. Further, the protocol prespecified that enrolment of patients with PAH associated with congenital heart disease could be stopped, either at a specific site or at all sites, if the number of such patients exceeded 50% of the total target population. Last, to maximise the global generalisability of the data, patient enrolment at a particular site could be stopped to prevent overrepresentation of one site.

The statistical analysis plan was designed to meet the registry objectives and was finalised before we did any analyses. For the aims of this report, analyses are descriptive. The populations analysed were the all-patients cohort, and the confirmed pulmonary hypertension cohort, which included only patients who met all enrolment criteria. We summarised continuous data using standard descriptive statistics—mean, SD, 95% CIs, and median, minimum, maximum, 25th and 75th percentiles—when appropriate, and categorical data using counts and percentages. The denominator for percentages was the total number of

patients with no missing data for each variable analysed. Missing data were not imputed. We calculated 95% CIs using the normal approximation for the binomial distribution. We did not do a formal sample size calculation and hence the sample was not powered a priori for specific comparisons. For formal statistical analyses, we examined categorical data with χ^2 tests and continuous data using analysis of variance (ANOVA). The assumptions underlying the ANOVA were checked and appropriate non-parametric analyses done when the assumption of normality was in doubt. We used SAS statistical software package (version 8.2 or higher) for the analyses. The cutoff date for data inclusion was Feb 15, 2010.

Role of the funding source

The TOPP registry is supported by a research grant from Actelion Pharmaceuticals. Actelion does not participate in the management of the registry, nor does it have access to the database, the individual sites, or patient data. The sponsor had no role in study design, analysis, interpretation of data, writing of the manuscript, or the decision to submit the paper for publication. All decisions related to the registry lie solely with the executive board of the Association for Pediatric Pulmonary Hypertension. The executive board decided to submit the paper for publication and wrote the report with contributions from all authors. All authors had access to the data and analyses. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From Jan 31, 2008, to Feb 15, 2010, 456 patients were enrolled. Enrolment of prevalent and incident patients was stopped at one site on Feb 10 and Aug 19, of 2009, respectively, to prevent overrepresentation of that site. Enrolment of prevalent patients at all other sites was stopped on May 22, 2009, to prevent such patients accounting for more than two-thirds of the total. No further predefined restriction rules were required.

Of the 456 patients in the all-patients cohort, 362 (79%) met all enrolment criteria for confirmed pulmonary hypertension, with 357 (99%) diagnoses based on right-heart catheterisation and five (1%) based on independently reviewed echocardiography and clinical records—of these five cases, three were further confirmed by histopathological findings. Of the confirmed pulmonary hypertension cases, about 30% were incident and about 70% were prevalent (table 1). The distribution of the all-patients cohort (456) was: Europe 157, Turkey 33, China 70, Japan 14, Australia 15, Brazil one, Mexico 21, USA 135, Canada ten. Of the 94 patients excluded from the confirmed pulmonary hypertension cohort, 11 did not meet haemodynamic criteria (six with mPAP<25 mm Hg or PVRI<3 WU/m^{-2}; five with mPCWP>12 mm Hg), and 83 did not have sufficient data to adequately calculate PVRi. Table 1 shows patient characteristics of each cohort. We recorded no apparent differences between patients in the confirmed pulmonary hypertension cohort and those excluded from that cohort.

In those with confirmed disease, the median age at diagnostic right-heart catheterisation was 7·0 years (IQR 3–12) with 61 patients (17%) diagnosed between 3 and 24 months of age, 111 (31%) between 2 and 6 years, 89 (25%) between 7 and 11 years, and 101 (28%) between 12 and 18 years. The average time from diagnostic right-heart catheterisation to enrolment was about 34 months in prevalent cases, and less than a month in incident cases (table 1). The mean time from onset of symptoms to diagnosis did not seem to differ between incident and prevalent cases, but tended to be longer when PAH was associated with congenital heart disease with unrepaired or residual systemic-to-pulmonary shunt and shorter in APAH not associated with congenital heart disease than in other subgroups (table 2).

PAH (group 1) and pulmonary hypertension associated with respiratory disorders or hypoxaemia (group 3) made up 88% (317) and 12% (42), respectively, of the confirmed pulmonary hypertension cohort (362). Only three patients (<1%) were in pulmonary hypertension group 4 or 5. There was an overall female preponderance (1·4 to 1) that was unchanged when stratified by incident or prevalent case, pulmonary hypertension group, PAH subgroup, or age. Of the 317 PAH patients, 57% had IPAH or FPAH and 36% had APAH associated with congenital heart disease (table 2). Most congenital heart disease cases (106 out 115, 93%) included systemic-to-pulmonary shunts. APAH associated with disorders other than congenital heart disease was reported in 6% of PAH patients (table 2). Bronchopulmonary dysplasia was the most frequent disorder associated with pulmonary hypertension group 3, present in 11 of 42 patients (26%). We recorded a significant association between the number of patients in each pulmonary hypertension group and age (p=0·01), with pulmonary hypertension group 3 disorders occurring more frequently in patients aged 3–24 months at diagnosis than in older age-at-diagnosis cohorts (15 aged 3–24 months, 25%; 12 aged 2–6 years, 11%; six aged 7–11 years, 7%; and nine aged 12–18 years, 9%).

We recorded comorbid disorders in 86 of 362 (24%) patients with confirmed pulmonary hypertension. Chromosomal disorder was most frequent (47, 13%) with 42 patients having trisomy 21. There was a significant association between trisomy 21 and pulmonary hypertension group (p=0·02). Trisomy 21 was present more often in patients with group 3 disorders (nine of 42, 21%) than in those with PAH (group 1, 32 of 317, 10%). Within the PAH cohort (317), trisomy 21 was present in 26 of 115 (23%) patients with APAH associated with congenital heart disease, five of 182 (3%) patients with IPAH or FPAH, and one of 20 (5%) patients with APAH not associated with congenital heart disease. In the remaining 44 patients, we recorded a spectrum of other chromosomal abnormalities, syndromes, and non-chromosomal anomalies.

Of the 362 patients with confirmed pulmonary hypertension, 21 (6%) had lived at an altitude greater than 2000 m for more than 6 months, 47 (13%) were premature (gestation <37 weeks), and eight (2%) had a history of persistent pulmonary hypertension of the newborn. In five of these eight, pulmonary hypertension seemed to persist and was confirmed by right-heart catheterisation (done at >3 months of age), whereas in the other three, the disorder was thought to have resolved during the neonatal period with PAH subsequently diagnosed by right-heart catheterisation. A history of bronchopulmonary dysplasia was reported in 17 of 362 patients (5%) and was regarded as the cause of the pulmonary hypertension by the treating physician in 11. Of the 362 patients, 34 (9%) had reactive airway disease, 23 (6%) had sleep disordered breathing or obstructive apnoeas (with obstructive sleep apnoea judged causative for the pulmonary hypertension in five), and 168 (46%) had a history of congenital heart disease, which was deemed causative for pulmonary hypertension in 115.

Family history was available in 320 of 362 patients with confirmed pulmonary hypertension. Family history for PAH was present in 21 of 182 patients with PAH without an associated disorder (12% FPAH) and in two of 20 patients with APAH not associated with congenital heart disease (10%). Genetic testing was done for 56 of the 317 patients with PAH, eight of whom (14%) had abnormal results—ie, four of the 29 IPAH (14%), two of the nine FPAH (22%), and two of the 18 APAH (11%) patients. Because of patient-privacy regulations, the abnormality cannot be disclosed in the registry.

The most frequently reported symptoms at presentation were dyspnoea on exertion and fatigue (table 3). Syncope was reported in 73 of 298 (25%) patients without shunt defined as either no history of a congenital systemic-to-pulmonary shunt, or a repaired congenital

systemic-to-pulmonary shunt without a residual shunt (in about 30% with IPAH or FPAH and in roughly 20% without shunt), but was not reported in any child with an unrepaired or residual congenital systemic-to-pulmonary shunt. A history of syncope was less frequent in the youngest age group at diagnosis (two aged 3–24 months; 3%) than in older age groups at diagnosis: 24 aged 2–6 years, 22%; 24 aged 7–11 years, 27%; and 23 aged 12–18 years, 23% (p=0·0006).

We recorded functional class at diagnosis for all patients. Irrespective of pulmonary hypertension group, most (230 [64%] of 362 patients with confirmed pulmonary hypertension) were in functional class I or II at diagnosis. The 6 min-walk test was reported in about 150 patients with confirmed pulmonary hypertension with a mean distance of roughly 420 m (table 2). This test was not done in children in the youngest age group (3–24 months), but was done in 23% (25) of children aged 2–6 years, 58% (52) of those aged 7–11 years, and 75% (76) of those aged 12–18 years at diagnosis.

Table 4 shows haemodynamic indices at diagnosis. Of 362 patients with confirmed pulmonary hypertension, 76 (21%) had cardiac index (ie, systemic blood flow) <2·5 L/min per m^2 (normal 2·5–4·0 L/min per m^2); 34 (9%) had mean right atrial pressure >12 mm Hg. Haemodynamics differed significantly between patients with PAH (group 1) and patients with pulmonary hypertension associated with respiratory disorders or hypoxaemia (group 3). mPAP, mean systemic arterial pressure (mSAP), mPAP to mSAP ratio, PVRi, systemic vascular resistance index (SVRi), PVRi to SVRi ratio, and resting systemic arterial oxygen saturation were all lower in patients in group 3 than in those with IPAH, FPAH, or APAH associated with congenital heart disease (table 4). Cardiac index was lower in patients with IPAH or FPAH than in those in group 3 (table 4). For PAH, systemic arterial oxygen saturation was lower for APAH associated with congenital heart disease than for IPAH or FPAH, but we recorded no other differences between these subgroups (table 4) nor clinically relevant differences in haemodynamics between IPAH and FPAH at diagnosis.

Discussion

Overall, about half the children enrolled with confirmed pulmonary hypertension had a history of congenital heart disease, which was regarded as causative for the PAH in most cases. In the most recent classification of pulmonary hypertension, a specific threshold for increased pulmonary vascular resistance was abandoned as a criterion for PAH.[11] Flow-associated pulmonary hyper tension due to large left-to-right systemic-to-pulmonary shunts might have normal pulmonary capillary wedge pressure and normal or even low pulmonary vascular resistance. In these patients (most often young children), early correction of the heart defect should lead to normalisation of pulmonary arterial pressure and prevent pulmonary vascular disease.[12] Because of the high proportion of APAH associated with congenital heart disease in group 1, awareness of the pulmonary vascular resistance criterion is important in the definition of this group. The TOPP registry therefore required pulmonary hypertension with increased PVRi (defined as >3WU/m^{-2}) to qualify for the confirmed pulmonary hypertension cohort.

Controlled studies assessing PAH drugs in APAH associated with congenital heart disease have been reported only in adults up to now.[13,14] Because some researchers have suggested that outcomes for this disorder are worse in children than in adults, most probably because of survival bias in adults,[15,16] the high proportion of such patients in paediatric pulmonary hypertension group 1 warrants directed study of safety and effectiveness of such drugs in this specific patient population.

The distribution of associated disorders in children in group 1 in TOPP differs from that reported in adults; although IPAH and FPAH account for about half the group 1 patients in both children and adults (57% in TOPP *vs* 43% in the French registry[3] and 49% in the US REVEAL registry[17]), APAH with congenital heart disease is more frequent in children than reported in European and US adult registries (36% of paediatric PAH *vs* 10–11% of adult PAH). PAH associated with connective tissue disease, HIV, drugs, or portopulmonary hypertension were very rare in TOPP (4% of all patients with confirmed pulmonary hypertension *vs* 38–41% in adults).[3,17] Additionally, chronic thromboembolic pulmonary hypertension (group 4) seems very rare in children. The female preponderance in TOPP (1·4 to 1 irrespective of age) is less than that reported in adults (2·4 to 1)[3,17] although an explanation for this difference is unclear.

We noted that bronchopulmonary dysplasia, which is associated with abnormal pulmonary vascular development,[18] was the most frequent disorder associated with pulmonary hypertension group 3. Pulmonary hypertension in infants with this disorder is associated with substantial morbidity and mortality.[19] Because of continued improvements in neonatal care, survival is increasing in premature infants of decreasing gestational age. Enhanced survival will probably be accompanied by an increase in bronchopulmonary dysplasia with new characteristics, including pulmonary hypertension.[18–20] The pathobiological features of pulmonary vascular disease in children with this disorder and its treatment approach are unclear and cannot be extrapolated from adults with group 3 disorders (eg, COPD).[21] Screening of children with broncho pulmonary dysplasia and dedicated studies are warranted.

Comorbidities were frequent in patients with confirmed pulmonary hypertension, with trisomy 21 the most prominent, especially in group 3 and APAH with congenital heart disease subgroups. Patients with trisomy 21 are at risk of developing pulmonary hypertension because they often have risk factors such as congenital heart disease and varied respiratory complications—eg, vascular, parenchymal, ventilatory, developmental, and immunological abnormalities.[22–25] These findings are highly relevant to the diagnostic assessment of pulmonary hypertension in such children. The high frequency of this anomaly in childhood pulmonary hypertension is of further interest because some results suggest reduced effectiveness of some PAH drugs in such children in group 1 with trisomy 21.[26]

We recorded syncope twice as often in TOPP as in adult studies (25% *vs* 12%).[27] It is a frequent presenting symptom in paediatric pulmonary hypertension, arising most often in children with IPAH or FPAH and in those without systemic-to-pulmonary shunts (or fully repaired shunts), whereas we did not record it in any child with an unrepaired or residual systemic-to-pulmonary shunt. In adults, syncope is an ominous sign, associated with sudden death if persistent despite treatment.[28] Longitudinal follow-up will determine whether persistent syncope on optimum therapy is associated with increased risk of sudden death in children.

The haemodynamic profile of paediatric pulmonary hypertension at diagnosis seen in TOPP was characterised by severly raised PAP and PVRi, yet preserved right-heart filling pressures and cardiac index. Consistent with these haemodynamics, most children were functional class I or II; 64% versus 25–44% in adults with group 1.[3,17] By contrast, the frequent increase in right-heart filling pressures and low cardiac index in adult patients with PAH are consistent with the predominance of functional class III. This paediatric profile, suggestive of a preserved cardiac performance despite severe pulmonary hypertension, could change as children grow into adults. These findings, underscoring the presence of advanced pulmonary hypertension despite good functional capacity, could affect early treatment strategies for this disorder in childhood.

Our findings suggest that 21% of paediatric patients who are judged to have pulmonary hypertension (and are frequently treated for this disorder) do not meet the haemodynamic criteria for such a diagnosis despite most having right-heart catheterisation. This situation arose most often because whether the child does or does not have increased pulmonary vascular resistance—a distinction of utmost importance—could not be determined from incomplete haemodynamics. These data suggest that education directed at an accurate diagnosis needs to be implemented for physicians assessing and treating children with suspected pulmonary hypertension.

TOPP has some limitations. Only specific centres participated, potentially resulting in unrecognised or severely ill patients not being seen at participating sites. Further, enrolment criteria might have introduced selection bias. The required right-heart catheterisation to confirm diagnosis could have led to underenrolment of patients with confirmed pulmonary hypertension. We attempted to minimise selection bias by consecutive patient enrolment at all sites. Because TOPP is not a population-based registry, incidence and prevalence cannot be estimated. We believe these limitations are outweighed by the sample size, its well defined enrolment criteria, its broad representation, and continuing longitudinal follow-up. Enrolment of consecutive incident cases continues at all sites until at least the end of 2013, with a minimum of 3 year follow-up from enrolment for all patients.

Acknowledgments

We thank Katherine Hutchinson of Quanticate UK for statistical analysis and Rita Locher, project manager, for continuous organisational support. The Association for Pediatric Pulmonary Hypertension, running the TOPP Registry, is supported by a research grant from Actelion Pharmaceuticals.

References

1. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2009; 54 (suppl 1):S43–54. [PubMed: 19555858]
2. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991; 115:343–49. [PubMed: 1863023]
3. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med. 2006; 173:1023–30. [PubMed: 16456139]
4. Frost AE, Badesch DB, Barst RJ, et al. The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US contemporary registries. Chest. 2011; 139:128–37. [PubMed: 20558556]
5. Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J. 2009; 30:2493–537. [PubMed: 19713419]
6. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension. A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc; and the Pulmonary Hypertension Association. J Am Coll Cardiol. 2009; 53:1573–619. [PubMed: 19389575]
7. Barst RJ, Ertel SI, Beghetti M, Ivy DD. Pulmonary arterial hypertension: a comparison between children and adults. Eur Respir J. 2011; 37:665–77. [PubMed: 21357924]
8. Berger RMF, Bonnet D. Treatment options in pediatric pulmonary arterial hypertension. Eur Respir Rev. 2010; 19:321–30. [PubMed: 21119191]

9. van Loon RL, Roofthooft MT, van Osch-Gevers M, et al. Clinical characterization of pediatric pulmonary hypertension: complex presentation and diagnosis. J Pediatr. 2009; 155:176–82. e171. [PubMed: 19524254]
10. Association for Pediatric Pulmonary Hypertension. [accessed Sept 30, 2011] Main objectives of the TOPP Disease Registry. https://www.peph-association.org/registry.jsp#objectives
11. Simonneau G, Galiè N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2004; 43 (suppl 12):S5–12.
12. van Loon RL, Roofthooft MT, Hillege HL, et al. Pediatric pulmonary hypertension in the Netherlands: epidemiology and characterization during the period 1991 to 2005. Circulation. 2011; 124:1755–64. [PubMed: 21947294]
13. Galiè N, Beghetti M, Gatzoulis MA, et al. Bosentan randomized trial of endothelin antagonist therapy-5 (BREATHE-5) investigators. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation. 2006; 114:48–54. [PubMed: 16801459]
14. Singh TP, Rohit M, Grover A, Malhotra S, Vijayvergiya R. A randomized, placebo-controlled, double-blind, crossover study to evaluate the efficacy of oral sildenafil therapy in severe pulmonary artery hypertension. Am Heart J. 2006; 151:851.e1–5. [PubMed: 16569546]
15. van Loon RL, Hoendermis ES, Duffels MG, et al. Long-term effect of bosentan in adults versus children with pulmonary arterial hypertension associated with systemic-to-pulmonary shunt: does the beneficial effect persist? Am Heart J. 2007; 154:776–82. [PubMed: 17893008]
16. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: the UK pulmonary hypertension service for children 2001–2006. Heart. 2009; 95:312–17. [PubMed: 18952635]
17. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL registry. Chest. 2010; 137:376–87. [PubMed: 19837821]
18. Stenmark KR, Abman SH. Lung vascular development: implications for the pathogenesis of bronchopulmonary dysplasia. Annu Rev Physiol. 2005; 67:623–61. [PubMed: 15709973]
19. Khemani E, McElhinney DB, Rhein L, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. Pediatrics. 2007; 120:1260–69. [PubMed: 18055675]
20. Jobe AH. The new bronchopulmonary dysplasia. Curr Opin Pediatr. 2011; 23:167–72. [PubMed: 21169836]
21. Kessler R, Faller R, Weitzenblum E, et al. Natural history of pulmonary hypertension in a series of 131 patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001; 164:219–24. [PubMed: 11463591]
22. Chi TPL, Krovetz J. The pulmonary vascular bed in children with Down syndrome. J Pediatr. 1975; 86:533–38. [PubMed: 123955]
23. McDowell KM, Craven DI. Pulmonary complications of Down syndrome during childhood. J Pediatr. 2011; 158:319–25. [PubMed: 20846671]
24. Marcus CL, Keens TG, Bautista DB, von Pechmann WS, Ward SL. Obstructive sleep apnea in children with Down syndrome. Pediatrics. 1991; 88:132–39. [PubMed: 1829151]
25. Cooney TP, Thurlbeck WM. Pulmonary hypoplasia in Down syndrome. N Engl J Med. 1982; 307:1170–73. [PubMed: 6214715]
26. Pfizer. [accessed Sept 30, 2011] Experience from the Revatio (sildenafil) pediatric program. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM220252.pdf
27. Le RJ, Fenstad ER, Maradit-Kremers H, et al. Syncope in adults with pulmonary arterial hypertension. J Am Coll Cardiol. 2011; 58:863–67. [PubMed: 21835323]
28. Rosenzweig EB, Barst RJ. Pulmonary arterial hypertension in children: a medical update. Curr Opin Pediatr. 2008; 20:288–93. [PubMed: 18475097]

Panel: Research in context

Systematic review

We searched Medline for studies describing clinical characteristics of paediatric pulmonary hypertension between Jan 1, 1997, and Sept 30, 2011, using the search terms “pulmonary hypertension”, “paediatric”, “childhood”, “cohort”, “registry”, and “clinical characteristics”. We excluded studies about neonatal pulmonary hypertension and those which selected patients on the basis of drug use. We identified 11 reports describing clinical characteristics at presentation in cohorts of 50 or more children with pulmonary hypertension. These reports studied eight different patient cohorts, derived from single centre studies (one), national networks (three) or registries (two), or regional, multicentre cardiac catheterisation registries (two). Results of these studies suggest that paediatric pulmonary hypertension presents with age-specific disease characteristics and clinical symptoms. However, generalisability of data from each of these studies is restricted by one or more limitations: small patient numbers (50–216), unclear enrolment criteria, insufficient disease characterisation, selection bias, non-exhaustive nature of the cohort, no representation of different pulmonary hypertension groups according to the clinical classification of pulmonary hypertension and, finally, the retrospective nature of each study.

Interpretation

As far as we are aware, the TOPP registry is the first global, prospective, centre-based, exhaustive, observational registry designed to provide present information about demographics, clinical characteristics, and outcome in paediatric pulmonary hypertension. With its large sample size from a real world population, its well defined enrolment criteria and broad representation, TOPP aims at global generalisability. We describe the clinical characteristics of paediatric pulmonary hypertension, and identify several age-specific characteristics, such as the type and distribution of associated disorders, the high prevalence of clinically relevant comorbidities (including chromosomal abnormalities), and the frequent reporting of syncope at presentation. These findings confirm previously suggested age-specific disease characteristics of paediatric pulmonary hypertension that impede direct extrapolation from adult data to childhood pulmonary hypertension and identify areas requiring specific attention and study. Longitudinal follow-up data from the TOPP registry will provide further insight into the specific characteristics, treatment effects, and outcomes in paediatric pulmonary hypertension.

Table 1

Demographic and clinical characteristics at diagnosis in all patients and in patients with confirmed pulmonary hypertension

	All patients	Patients with confirmed pulmonary hypertension		
		All	Incident	Prevalent
Patients	456 (100%)	362 (79%)	102 (28%)	260 (72%)
Female	268 (59%)	214 (59%)	58 (57%)	156 (60%)
Preterm	63 (14%)	47 (13%)	16 (16%)	31 (12%)
Age at diagnosis (years)	7·1 (6·6–7·6)	7·5 (7·0–8·1)	8·5 (7·5–9·5)	7·2 (6·5–7·8)
Weight (kg)	26·5 (24·7–28·4)	28·0 (25·9–30·1)	30·8 (26·7–35·0)	26·8 (24·4–29·3)
Height (cm)	117 (114–120)	119 (116–123)	124 (118–131)	117 (113–121)
BMI (kg/m^2)	17·05 (16·63–17·48)	17·21 (16·74–17·68)	17·68 (16·67–18·69)	17·02 (16·50–17·54)
BSA (m^2)	0·93 (0·88–0·97)	0·94 (0·90–0·99)	1·02 (0·93–1·11)	0·91 (0·86–0·97)
Ethnicity	454 (100%)	362 (100%)	102 (100%)	260 (100)
White or Hispanic	302 (67%)	229 (63%)	57 (56%)	172 (66%)
Black	14 (3%)	8 (2%)	5 (5%)	3 (1%)
Asian	107 (24%)	99 (27%)	33 (32%)	66 (25%)
Other	15 (3%)	13 (4%)	5 (5%)	8 (3%)
Unknown	16 (4%)	13 (4%)	2 (2%)	11 (4%)
Time from onset symptoms to diagnosis (months)	17 (15–20)	17 (14–20)	24 (16–31)	15 (12–18)
Median (IQR)	6 (2–19)	6 (2–19)	6 (3–38)	5 (1–17)
Time from diagnosis to enrolment (months)	24·0 (21·7–26·4)	24·4 (21·8–27·1)	0·7 (0·5–0·9)	33·7 (30·7–36·7)
Median (range)	13·7 (1·7–39·8)	14·1 (2·3–39·8)	0·2 (0·0–1·1)	28·5 (12·6–48·9)
Group 1*	398 (87%)	317 (88%)	88 (86%)	229 (88%)
IPAH or FPAH	212 (53%)	182 (57%)	55 (63%)	127 (55%)
APAH-congenital heart disease	160 (40%)	115 (36%)	26 (30%)	89 (39%)
Systemic-to-pulmonary shunt	150 (38%)	107 (34%)	25 (28%)	82 (36%)
Unrepaired	91 (23%)	61 (19%)	14 (16%)	47 (21%)
Repaired	57 (14%)	45 (14%)	10 (11%)	35 (15%)
Never shunt	12 (3%)	9 (3%)	2 (2%)	7 (3%)
Repaired left obstruction	7 (2%)	7 (2%)	1 (1%)	6 (3%)
APAH-connective tissue disease	10 (3%)	9 (3%)	1 (1%)	8 (3%)
APAH-chronic liver disease	4 (1%)	2 (1%)	0 (0%)	2 (1%)
APAH-HIV	0 (0%)	0 (0%)	0 (0%)	0 (0%)
APAH-drugs or toxins	0 (0%)	0 (0%)	0 (0%)	0 (0%)
APAH-HHT	2 (1%)	1 (<1%)	1 (1%)	0 (0%)
APAH-thyroid	2 (1%)	1 (<1%)	0 (0%)	1 (<1%)

	All patients	Patients with confirmed pulmonary hypertension		
		All	Incident	Prevalent
APAH-other	3 (1%)	3 (1%)	0 (0%)	3 (1%)
PVOD or PCH	6 (2%)	6 (2%)	4 (5%)	2 (1%)
None of the above	5 (1%)	3 (1%)	2 (2%)	1 (<1%)
Group 3 *	52 (11%)	42 (12%)	13 (13%)	29 (11%)
Bronchopulmonary dysplasia	17 (33%)	11 (26%)	3 (23%)	8 (28%)
Interstititial lung disease	12 (23%)	10 (24%)	4 (31%)	6 (21%)
High altitude	7 (13%)	7 (17%)	3 (23%)	4 (14%)
Congenital diaphragmatic hernia	6 (12%)	4 (10%)	1 (8%)	3 (10%)
Congenital pulmonary hypoplasia	7 (13%)	5 (12%)	2 (15%)	3 (10%)
Disordered breathing or OSAS	5 (10%)	5 (12%)	0 (0%)	5 (17%)
Kyphoscoliosis	2 (4%)	2 (5%)	0 (0%)	2 (7%)
Other	2 (4%)	2 (5%)	1 (8%)	1 (3%)
Groups 4 or 5 *	4 (1%)	3 (1%)	1 (1%)	2 (1%)
WHO Functional Class	449 (98%)	362 (100%)	102 (100%)	260 (100%)
I	54 (12%)	45 (12%)	11 (11%)	34 (13%)
II	212 (47%)	185 (51%)	52 (51%)	133 (51%)
III	146 (33%)	108 (30%)	28 (27%)	80 (31%)
IV	37 (8%)	24 (7%)	11 (11%)	13 (5%)
6 min walk test	175 (38%)	153 (42%)	46 (45%)	107 (41%)
Metres (mean [95% CI])	407 (389–426)	417 (398–436)	445 (414–476)	405 (381–429)

Data are n (%) or mean (95% CI) unless otherwise specified. Incident cases were those diagnosed within 3 months of enrolment. Prevalent cases were those diagnosed more than 3 months before enrolment. Two patients are missing for pulmonary hypertension classification because of missing data. Patients could be counted in more than one APAH disease category and in more than one associated disease category for group 3. BMI=body-mass index. BSA=body surface area. IPAH=idiopathic pulmonary arterial hypertension. FPAH=familial pulmonary arterial hypertension. APAH=pulmonary arterial hypertension associated with other disorders. HHT=hereditary haemorrhagic teleangiectasia. PVOD=pulmonary veno-occlusive disease. PCH=pulmonary capillary haemangiomatosis. OSAS=obstructive sleep apnoea syndrome.

* Classified according to (3rd World Pulmonary Hypertension Symposium[11]).

Table 2

Demographic and clinical characteristics at diagnosis in patients with confirmed pulmonary hypertension (PH confirmed) diagnosis according to pulmonary hypertension groups and subgroups

	All PH confirmed	PH group 3	PH group 1					
			IPAH or FPAH	APAH with CHD				APAH excluding APAH with CHD
				All CHD	Unrepaired shunt*	Repaired shunt	Never shunt	
Patients	362 (100%)	42 (100%)	182 (100%)	115 (100%)	61 (100%)	45 (100%)	9 (100%)	20 (100%)
Female	214 (59%)	26 (62%)	109 (60%)	66 (57%)	38 (62%)	25 (56%)	3 (33%)	11 (55%)
Preterm	47 (13%)	18 (43%)	14 (8%)	11 (10%)	5 (8%)	6 (13%)	0 (0%%)	4 (20%)
Age at diagnosis (years) (mean [95% CI])	7·5 (7·0–8·1)	5·5 (3·7–7·3)	7·6 (6·9–8·3)	7·7 (6·7–8·8)	8·4 (6·9–9·9)	7·4 (5·8–8·9)	4·8 (0·6–9·0)	10·0 (7·5–12·4)
Incident patients	102 (28%)	13 (31%)	55 (30%)	26 (23%)	14 (23%)	10 (22%)	2 (22%)	7 (35%)
Ethnicity	362 (100)	42 (100)	182 (100)	115 (100)	61 (100)	45 (100)	9 (100)	20 (100)
White or Hispanic	229 (63%)	35 (83%)	118 (65%)	65 (57%)	35 (57%)	28 (62%)	2 (22%)	8 (40%)
Black	8 (2%)	0 (0%)	5 (3%)	2 (2%)	2 (3%)	0 (0%)	0 (0%)	1 (5%)
Asian	99 (27%)	3 (7%)	48 (26%)	40 (35%)	23 (38%)	12 (27%)	5 (56%)	8 (40%)
Other	13 (4%)	2 (5%)	5 (3%)	3 (3%)	1 (2%)	2 (4%)	0 (0%)	3 (15%)
Unknown	13 (4%)	2 (5%)	6 (3%)	5 (4%)	0	3 (7%)	2 (22%)	0 (0%)
Time from onset symptoms to diagnosis (months) (mean [95% CI])	17 (14–20)	16 (7–25)	15 (11–19)	24 (17–32)	30 (16–44)	19 (11–26)	22 (4–40)	5 (1–8)
Median (IQR)	6 (2–19)	4 (1–20)	5 (1–17)	9 (4–29)	10 (3–28)	8 (4–25)	9 (7–45)	3 (1–4)
Time from diagnosis to enrolment (months) (mean [95% CI])	24 (22–27)	25 (18–32)	25 (21–29)	24 (19–28)	23 (16–29)	25 (18–32)	24 (3–46)	16 (6–27)
Median (IQR)	14 (2–40)	22 (2–40)	15 (1–43)	14 (4–41)	13 (4–36)	19 (6–45)	20 (4–26)	8 (1–23)
WHO functional class	362 (100%)	42 (100%)	182 (100%)	115 (100%)	61 (100%)	45 (100%)	9 (100%)	20 (100%)
I	45 (12%)	8 (19%)	28 (15%)	8 (7%)	2 (3%)	4 (9%)	2 (22%)	1 (5%)
II	185 (51%)	20 (48%)	84 (46%)	72 (63%)	40 (66%)	28 (62%)	4 (44%)	8 (40%)
III	108 (30%)	13 (31%)	55 (30%)	31 (27%)	18 (30%)	13 (29%)	0 (0%)	7 (35%)
IV	24 (7%)	1 (2%)	15 (8%)	4 (3%)	1 (2%)	0 (0%)	3 (33%)	4 (20%)

	All PH confirmed	PH group 3	PH group 1					
			IPAH or FPAH	APAH with CHD				APAH excluding APAH with CHD
				All CHD	Unrepaired shunt*	Repaired shunt	Never shunt	
6 min walk test	153 (42%)	10 (24%)	83 (46%)	50 (43%)	30 (49%)	19 (42%)	1 (11%)	9 (45%)
Metres (mean [95% CI])	417 (398–436)	466 (352–580)	407 (379–434)	422 (393–452)	420 (385–456)	429 (370–488)	355 (NC)	427 (330–525)

Patients from pulmonary hypertension groups 4 and 5 (n=3), included in all patients with confirmed pulmonary hypertension, are not depicted separately in this table. APAH=pulmonary arterial hypertension associated with other disorders. IPAH=idiopathic pulmonary arterial hypertension. FPAH=familial pulmonary arterial hypertension. CHD=congenital heart disease. NC=not calculated.

*Or partial repair.

Table 3

Clinical symptoms at diagnosis, reported for 5% or more of all patients with confirmed pulmonary hypertension (PH confirmed), according to pulmonary hypertension groups and subgroups

	All PH confirmed	PH group 3	PH group 1					
			IPAH or FPAH	APAH with congenital heart disease				APAH excluding APAH with CHD
				All CHD	Unrepaired shunt*	Repaired shunt	Never shunt	
Patients	362 (100%)	42 (100%)	182 (100%)	115 (100%)	61 (100%)	45 (100%)	9 (100%)	20 (100%)
Dyspnoea with exertion	235 (65%)	22 (52%)	121 (66%)	77 (67%)	48 (79%)	24 (53%)	5 (56%)	14 (70%)
Fatigue	149 (41%)	12 (29%)	82 (45%)	47 (41%)	29 (48%)	13 (29%)	5 (56%)	6 (30%)
Syncope	73 (20%)	3 (7%)	57 (31%)	10 (9%)	0 (0%)	8 (18%)	2 (22%)	3 (15%)
Cyanosis with exertion	64 (18%)	10 (24%)	24 (13%)	27 (23%)	22 (36%)	5 (11%)	0 (0%)	3 (15%)
Cough	48 (13%)	6 (14%)	32 (18%)	8 (7%)	1 (2%)	7 (16%)	0 (0%)	2 (10%)
Cyanosis with rest	44 (12%)	11 (26%)	7 (4%)	22 (19%)	15 (25%)	4 (9%)	3 (33%)	4 (20%)
Dyspnoea with rest	39 (11%)	12 (29%)	13 (7%)	11 (10%)	3 (5%)	6 (13%)	2 (22%)	3 (15%)
Chest pain or discomfort	39 (11%)	3 (7%)	24 (13%)	7 (6%)	4 (7%)	2 (4%)	1 (11%)	4 (20%)
Near-syncope	28 (8%)	1 (2%)	21 (12%)	5 (4%)	1 (2%)	4 (9%)	0 (0%)	1 (5%)
Dizziness	25 (7%)	2 (5%)	14 (8%)	6 (5%)	4 (7%)	2 (4%)	0 (0%)	2 (10%)
Palpitations	22 (6%)	0 (0%)	12 (7%)	6 (5%)	6 (10%)	0 (0%)	0 (0%)	3 (15%)
Pallor with exertion	17 (5%)	3 (7%)	8 (4%)	5 (4%)	5 (8%)	0 (0%)	0 (0%)	0 (0%)
Irritability	17 (5%)	5 (12%)	8 (4%)	3 (3%)	2 (3%)	1 (2%)	0 (0%)	1 (5%)

Data are number (%). Patients from pulmonary hypertension groups 4 and 5 (n=3), included in all patients with confirmed pulmonary hypertension, are not depicted separately in this table. Full details are provided in the webappendix. APAH=pulmonary arterial hypertension associated with other disorders. IPAH=idiopathic pulmonary arterial hypertension. FPAH=familial pulmonary arterial hypertension. CHD=congenital heart disease.

*Or partial repair.

Table 4

Haemodynamic characteristics at diagnosis in patients with confirmed pulmonary hypertension (PH confirmed), according to pulmonary hypertension groups and subgroups

	All patients with PH confirmed	PH group 3	PH group 1					
			IPAH or FPAH	APAH with CHD				APAH excluding APAH with CHD
				All CHD	Unrepaired shunt*	Repaired shunt	Never shunt	
Patients with heart catheterisation at diagnosis	357 (99%)	42 (100%)	178 (98%)	115 (100%)	61 (100%)	45 (100%)	9 (100%)	19 (95%)
mRAP	345 (95%)	41 (98%)	172 (95%)	110 (96%)	59 (97%)	43 (96%)	8 (89%)	19 (95%)
Mean mm Hg (95% CI)	7 (7–8)	7 (6–8)	7 (6–8)	7 (7–8)	7 (6–8)	8 (7–9)	10 (5–14)	8 (6–9)
p value†	..	..	0·73	..	..	..	..	..
mPAP	357 (99%)	42 (100%)	178 (98%)	115 (100%)	61 (100%)	45 (100%)	9 (100%)	19 (95%)
Mean mm Hg (95% CI)	58 (56–59)	44 (39–48)	59 (57–62)§	61 (57–64)§	64 (59–69)	56 (49–62)	62 (49–75)	53 (45–61)
p value†	..	..	<0·0001	..	..	..	..	..
mPCWP	357 (99%)	42 (100%)	178 (98%)	115 (100%)	61 (100%)	45 (100%)	9 (100%)	19 (95%)
Mean mm Hg (95% CI)	8 (8–9)	9 (8–9)	8 (8–9)	9 (8–9)	8 (8–9)	9 (8–10)	8 (6–11)	8 (7–9)
p value†	..	..	0·99	..	..	..	..	..
mSAP	353 (98%)	42 (100%)	176 (97%)	113 (98%)	59 (97%)	45 (100%)	9 (100%)	19 (95%)
Mean mm Hg (95% CI)	68 (66–69)	62 (58–67)	68 (66–70)§	68 (65–70)§	66 (62–70)	68 (64–72)	74 (66–81)	74 (66–82)
p value†	..	..	0·04	..	..	..	..	..
Cardiac index	348 (96%)	41 (98%)	175 (96%)	110 (96%)	56 (92%)	45 (100%)	9 (100%)	19 (95%)
Mean L/min/m^2 (95% CI)	3·7 (3·5–3·8)	4·2 (3·6–4·8)	3·4 (3·2–3·6)§	3·9 (3·5–4·3)	3·8 (3·3–4·3)	3·7 (3·2–4·2)	5·4 (2·6–8·3)	4·0 (2·8–5·2)
p value‡	..	..	0·02	..	..	..	..	..
Qp:Qs	357 (99%)	42 (100%)	182 (100%)	110 (96%)	56 (92%)	45 (100%)	9 (100%)	20 (100%)
Ratio median (IQR)	1·00 (1·0–1·0)	1·00 (1·0–1·0)	1·00 (1·0–1·0)	1·00 (1·0–1·1)	1·03 (0·8–1·5)	1·00 (1·0–1·0)	1·00 (1·0–1·0)	1·00 (1·0–1·0)
p value‡	..	..	0·92	..	..	..	..	..
mPAP:mSAP	353 (98%)	42 (100%)	176 (97%)	113 (98%)	59 (97%)	45 (100%)	9 (100%)	19 (95%)

	All patients with PH confirmed	PH group 3	PH group 1					
			IPAH or FPAH	APAH with CHD				APAH excluding APAH with CHD
				All CHD	Unrepaired shunt*	Repaired shunt	Never shunt	
Ratio median (IQR)	0·86 (0·7–1·0)	0·69 (0·6–1·0)	0·87 (0·7–1·0)§	0·92 (0·8–1·0)§	0·96 (0·9–1·1)	0·84 (0·6–1·0)	0·85 (0·8–1·0)	0·64 (0·5–1·1)
p value†	..	..	0·0001	..	..	..	..	..
PVRi	357 (99%)	42 (100%)	178 (98%)	115 (100%)	61 (100%)	45 (100%)	9 (100%)	19 (95%)
Mean WU/m^{-2} (95% CI)	16·0 (14·9–17·0)	9·8 (8·1–11·5)	17·2 (15·8–18·6)§	16·3 (14·3–18·3)§	16·8 (14·6–19·0)	15·0 (11·7–18·3)	19·3 (4·0–34·7)	14·9 (11·1–18·7)
p value‡	..	..	<0·001	..	..	..	..	..
SVRi	340 (94%)	41 (98%)	169 (93%)	108 (94%)	54 (89%)	45 (100%)	9 (100%)	19 (95%)
Mean WU/m^{-2} (95% CI)	19·7 (18·7–20·8)	15·8 (13·2–18·3)	20·5 (19·2–21·8)§	19·0 (17·2–20·8)§	19·0 (16·6–21·4)	18·6 (16·4–20·8)	20·8 (6·4–35·1)	23·4 (14·3–32·4)
p value‡	..	..	0·002	..	..	..	..	..
PVRi:SVRi	340 (94%)	41 (98%)	169 (93%)	108 (94%)	54 (89%)	45 (100%)	9 (100%)	19 (95%)
Ratio median (IQR)	0·80 (0·6–1·0)	0·66 (0·5–1·0)	0·82 (0·6–1·0)§	0·79 (0·6–1·0)§	0·82 (0·6–1·2)	0·79 (0·5–1·0)	0·89 (0·7–1·0)	0·64 (0·4–1·1)
p value‡	..	..	0·02	..	..	..	..	..
Sys ven SO_2	202 (56%)	30 (71%)	72 (40%)	88 (77%)	59 (97%)	27 (60%)	2 (22%)	10 (50%)
Mean % (95% CI)	66% (65–67)	66% (63–70)	66% (64–68)	66% (64–68)	66% (64–69)	65% (61–69)	75% (71–79)	64% (56–72)
p value†	..	..	0·96	..	..	..	..	..
Sys art SO_2	214 (59%)	32 (76%)	78 (43%)	91 (79%)	60 (98%)	29 (64%)	2 (22%)	11 (55%)
Mean % (95% CI)	91% (90–92)	86% (81–91)	94% (93–95)§	90% (88–92)§†¶	88% (87–90)	93% (91–96)	91% (··)	88% (81–96)
p value†	..	..	<0·0001	..	..	..	..	..
Yes responders at AVT	117 (36)	21 (51)	61 (38)	25 (25)	12 (22)	13 (33)	0 (%)	8 (42)
No responders at AVT	206 (64)	20 (49)	100 (62)	74 (75)	42 (78)	26 (67)	6 (100)	11 (58)

APAH excluding APAH with congenital heart disease and groups 4 and 5 are excluded from the analysis. Only patients in the confirmed pulmonary hypertension population are included in the analysis. Patients from pulmonary hypertension groups 4 and 5 (n=3), included in all patients with confirmed pulmonary hypertension, are not depicted separately in this table. APAH=pulmonary arterial hypertension associated with other disorders. IPAH=idiopathic pulmonary arterial hypertension. FPAH=familial pulmonary arterial hypertension. mRAP=mean right atrial pressure. mPAP=mean pulmonary arterial pressure. mSAP=mean systemic arterial pressure. mPCWP=mean pulmonary capillary wedge pressure. PVRI=pulmonary vascular resistance indexed. SVRI=systemic vascular resistance indexed. Qp=pulmonary blood flow. Qs=systemic blood flow. Sys ven SO_2=systemic venous oxygen saturation. Sys art SO_2=systemic arterial oxygen saturation. AVT=acute pulmonary vasoresponse test as reported by the treating physician (no predefined criteria were used). Data are number (%) unless otherwise specified.

[*] Or partial repair.

[†] p value from ANOVA with cause subgroup (1=pulmonary hypertension group 3, 2=IPAH or FPAH, 3=all congenital heart disease) included in the model. APAH excluding APAH with congenital heart disease and groups 4 and 5 are excluded from the analysis. Only patients in the confirmed pulmonary hypertension population are included in the analysis.

[‡] p value from Kruskal-Wallis test to assess differences across cause subgroups (1=pulmonary hypertension group 3, 2=IPAH or FPAH, 3=all congenital heart disease).

[§] Significantly different from PH Group 3.

[¶] Significantly different from IPAH or FPAH.