Update from the World Symposium on Pulmonary Hypertension 2018: does the new hemodynamic definition of pediatric pulmonary hypertension have an impact on treatment strategies?

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Abstract: Pediatric pulmonary arterial hypertension (PAH) is a progressive life-threatening disease of the pulmonary vasculature and is defined as an elevation of the mean pulmonary arterial pressure. Before the 6th World Symposium on Pulmonary Hypertension (WSPH) in 2018, pulmonary hypertension (PH) used to be defined as a mean pulmonary artery pressure (mPAP) of ≥25 mmHg. On the WSPH a revised hemodynamic definition of PH was introduced lowering the threshold for a normal mPAP from <25 to <21 mmHg. The Pediatric Task Force chose to follow this newly proposed definition of PH in order to speak a uniform language and facilitate transition to adult services. In this opinion paper we discuss the rationale behind the new PH definition and the impact on pediatric PH. We conclude, that to date, there is no evidence in children, suggesting that this decrease of threshold for PH warrants any further measures than clinical outpatient-follow-up. Hitherto, the new definition does not impact on currently applicable treatment strategies in children with PH.

Keywords: Pediatric pulmonary hypertension (pediatric PH); World Symposium on Pulmonary Hypertension 2018 (WSPH 2018); definition; (targeted) advanced therapy

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Introduction

Pulmonary hypertension (PH) is characterized by an elevation of the pulmonary arterial pressure and is associated with different underlying diseases affecting the pulmonary vasculature. While there is increased evidence for genetic factors playing a causative role, predisposing an individual to the phenotype and development of PH, underlying etiologies, triggers and driving factors vary. Etiologies in children comprise pathologies of the lung parenchyma or interstitial changes and uncorrected cardiac shunt lesions with increased pulmonary blood flow, that may lead to pulmonary vascular disease. In addition, structural lesions of the left heart or myocardial dysfunction can potentially cause postcapillary PH.

The most frequent forms of PH in childhood are idiopathic pulmonary arterial hypertension (IPAH)/hereditary pulmonary hypertension (HPAH) and PAH associated with congenital heart disease (PAH-CHD) (1).

According to international guidelines, PH used to be defined as elevation of the mean pulmonary artery pressure (mPAP) ≥25 mmHg. Due to variability in pulmonary hemodynamics during the postnatal adaptation process, pediatric PH was formerly defined as mPAP ≥25 mmHg in children >3 months of age. In pediatric PH, particularly in patients with associated PH-CHD, it is recommended to use the indexed pulmonary vascular resistance (PVRI) to assess the presence of pulmonary vascular hypertensive disease (PVHD), defined as PVRI ≥3 wood units×m^2 (WU×m^2) (*Table 1*).

Table 1 Definitions of PH in children and adolescents

PH	mPAP >20 mmHg in children >3 months at sea level
Precapillary PH (i.e., PAH)	mPAP >20 mmHg; PAWP or LVEDP ≤15 mmHg; PVRI ≥3 WU×m^2 (diastolic TPG ≥7 mmHg as adjunct criterion)
Isolated postcapillary PH	mPAP >20 mmHg; PAWP or LVEDP >15 mmHg; PVRI <3 WU×m^2
Combined pre- and postcapillary PH	mPAP >20 mmHg; PAWP or LVEDP >15 mmHg; PVRI ≥3 WU×m^2
PAH	mPAP >20 mmHg; PAWP or LVEDP ≤15 mmHg; PVRI ≥3 WU×m^2
PHVD	Congenital heart defects: normal circulation: mPAP >20 mmHg and PVRI ≥3 WU×m^2; univentricular palliation: (e.g., Fontan-circulation): mean TPG* >6 mmHg or PVRI >3 WU×m^2

Modified according to reference (2). *mPAP–mLAP or PAWP, PH, pulmonary hypertension; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; LVEDP, left ventricular end diastolic pressure; PVRI, pulmonary vascular resistance index; TPG, transpulmonary pressure gradient; WU, wood units[#]; PHVD, pulmonary hypertensive vascular disease; mLAP, mean left atrial pressure. [#], Traditional unit of vascular resistance.

The updated PH definition

During the latest World Symposium on Pulmonary Hypertension (WSPH) 2018 in Nice, it was proposed, that the mPAP threshold to define PH should be lowered from ≥25 to >20 mmHg (3).

Additionally to the criterion to determine precapillary PH of a left ventricular end diastolic pressure (LVEDP) or pulmonary capillary wedge pressure (PCWP) ≤15 mmHg, the PVRI as adjunct variable was added to this definition (4).

The rationale for lowering the mPAP threshold is based on register studies of adult PH patients which revealed higher mortality yet with these lower mPAP levels (5,6).

This new definition (mPAP >20 mmHg) has also been accepted by the Pediatric Task Force of the WSPH, in order to speak a common language and facilitate transition to adult services (4). However this was not uniformly welcomed by all pediatric cardiologists as concerns existed that the new definition may lead to overdiagnosis and overtreatment of PH.

The new definition has already been appreciated and found entry to the updated consensus document of the "European Pediatric Pulmonary Vascular Disease Network" published in 2019 (2). However, to date there are no pediatric data, to suggest that a mild elevation of the mPAP of 21–24 mmHg (according to the new definition) has similar impact in children as in adults (2,4).

In most children, who are diagnosed even at a young age with idiopathic PH, mPAPs do well exceed these values anyhow. Other pediatric PH subgroups may present with lower levels of mPAP (21–24 mmHg), who are now being categorized with the diagnosis of PH. This may apply particularly for infants with chronic lung disease (CLD)/bronchopulmonary dysplasia (BPD), who can present with variable levels of PH severity. But even for those children, to date there is no data to suggesting a necessity to treat patients with mPAP <25 mmHg. Treatment initiation at these lower levels of PH warrants careful judgement and consideration of comorbidities.

Particularly children with an associated congenital cardiac shunt (e.g., atrial- or ventricular septal defect or persistent arterial duct) may show a prolonged period of cardiopulmonary adaptation with a slower decrease in PVR compared to infants without a shunt defect. Those infants with a congenital heart defect and a significant shunt benefit most from a timely intervention and shunt closure, to abolish the extra strain on the pulmonary vasculature, avoid PVHD progression due to an increased pulmonary blood flow. If other risk factors for PH and an increased likelihood of persistence of problems are present, that could at least in part contribute to high pulmonary artery pressures, fenestrated closure should be considered.

Only a minority of patients will develop PH postoperatively with a chronically increased PVR and PHVD later, when shunt closure occurs early in life (7). However, patients, who develop PH, sometimes even decades after corrective surgery, have been shown to have a significantly increased mortality risk (2,7,8).

Implications of new definition

A change of definition of a disease raises the question,

if this results in a change of the therapeutic approach, particularly for asymptomatic patients. Not only the indication, but also the economic burden and potential associated adverse effects of the drugs have to be taken into account (7).

Due to scarcity of randomized controlled studies, evidence-based therapeutic strategies in children with PH are lacking and experience if often adopted from adult practice. In addition, there is a lack of licensed advanced therapeutic drugs for the use in children. Hence off-label therapy is often used in children, in analogy to other pediatric subspecialties (9).

In contrast to the longest available vasodilators, the calcium-channel-blockers, the—so called—'advanced medical therapies' do not only have vasodilatory effects, but are also thought to have anti-proliferative properties and hence may slow down disease progression and vascular remodeling processes that lead to PHVD.

To date there is no evidence for an improved outcome or hemodynamic improvement with the use of advanced anti-pulmonary hypertensive therapies with only a mildly elevated mPAP of 21–24 mmHg.

However, also the previous threshold for the PH definition of mPAP ≥25 mmHg has been an arbitrary choice. All available studies on PAH-drug safety and efficacy have investigated exclusively patients with a mPAP ≥25 mmHg, according to the former definition. Yet even available pediatric studies were designed enrolling children according to the former definition. Thus, evidence for efficacy, functional or prognostic benefit of advanced therapeutic drugs provide data specifically for those children, who represent a different population.

In our opinion, the use of advanced therapies on the basis of the new definition (mPAP >20 mmHg) is questionable. To date, in most children and teenagers with PH advanced medical therapy is still only warranted if mPAP exceeds ≥25 mmHg. Indication for treatment, however, should be a patient-tailored decision, depending on PH etiology and other associated driving factors.

We believe, it is justified, to offer follow-up and screening visits for children and adolescents, who do fulfil the PH criteria according to the new definition (10,11).

For individual (symptomatic) patients with an only mildly elevated mPAP (21–24 mmHg) and increase of PVRI (≥3 WU×m^2) or associated risk factors (e.g., positive genetics and/or family history of severe PH), advanced medical therapy may be indicated.

Because of the complexity and heterogeneity of PH in childhood and adolescence, children should be referred to pediatric cardiology centers, that have PH expertise. Particularly the indication for PAH specific therapy—independent of clinical severity at presentation—should be initiated there and children should be linked to and seen in PH specialist clinics. Counselling patients and parents of the implication of the new PH definition (mPAP >20 mmHg) is paramount. To date there are no therapeutic consequences in patients, who may present with mPAPs between 21–24 mmHg during cardiac catheterization, which formally confirms the diagnosis of PH according to the new definition.

Conclusions

The definition of PH has changed in 2018 (WSPH, Nice) to a lower mPAP of >20 mmHg (rather than ≥25 mmHg previously). Because of lacking evidence in children, no changes to currently applied pharmaceutical strategies are warranted to date.

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References

1. Berger RM, Beghetti M, Humpl T, et al. Clinical features of paediatric pulmonary hypertension: a registry study. Lancet 2012;379:537-46.
2. Hansmann G, Koestenberger M, Alastalo TP, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J Heart Lung Transplant 2019;38:879-901.
3. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53:1801913.
4. Rosenzweig EB, Abman SH, Adatia I, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J 2019;53:1801916.
5. Douschan P, Kovacs G, Avian A, et al. Mild Elevation of Pulmonary Arterial Pressure as a Predictor of Mortality. Am J Respir Crit Care Med 2018;197:509-16.
6. Kolte D, Lakshmanan S, Jankowich MD, et al. Mild Pulmonary Hypertension Is Associated With Increased Mortality: A Systematic Review and Meta-Analysis. J Am Heart Assoc 2018;7:e009729.
7. Lammers AE, Bauer LJ, Diller GP, et al. Pulmonary hypertension after shunt closure in patients with simple congenital heart defects. Int J Cardiol 2020;308:28-32.
8. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001-2006. Heart 2009;95:312-7.
9. Hansmann G, Apitz C. Treatment of children with pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016;102 Suppl 2:ii67-85.
10. Apitz C, Hansmann G, Schranz D. Hemodynamic assessment and acute pulmonary vasoreactivity testing in the evaluation of children with pulmonary vascular disease. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016;102 Suppl 2:ii23-9.
11. Koestenberger M, Hansmann G, Apitz C, et al. Diagnostics in Children and Adolescents with Suspected or Confirmed Pulmonary Hypertension. Paediatr Respir Rev 2017;23:3-15.

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