



Pediatric pulmonary hypertension

Pulmonary hypertension (PH) is a life-threatening disease and is characterized by pathological elevation of pulmonary pressure and associated with a heterogeneous spectrum of diseases affecting the pulmonary vasculature (1).

The care of patients with PH is a medical specialty in constant flux and shifting paradigms. There are new drugs, changing treatment strategies, renaissance of already almost forgotten surgical techniques like the Potts' shunt and last but not least improved outcome after lung transplantation as last resource for these patients.

Despite all available guidelines and recommendations, counselling remains challenging and often has to be patient tailored.

Although available treatment options have transformed the outcome of these patients, there is still a long way to go. In this series, we focus on PH in children. While pathobiology and clinical features share similarities in children and adults, pediatric PH provides many differences to adult disease, which need to be considered to provide best possible care for this challenging patient population (*Figure 1*).

The idea for this special series came from a very successful symposium on Pediatric Pulmonary Hypertension which took place in Münster in 2019 organized by Dr. Astrid Lammers in her role as head of the German Working Group of Pediatric Pulmonary Hypertension. Most of the invited speakers, all of them well-known experts in this field, were happy to accept our invitation to write an updated manuscript of their talks. And so, we are now proud to present this special series with the great support of the Editors of *CDT*.

We open with a tribute to Sheila Glennis Haworth, who sadly died in 2020. She actively contributed to our symposium in Münster by giving us the honor presenting the opening lecture on “Lung development and pathogenesis of pulmonary vascular disease”. She has been a true pioneer, has participated in the last important decades with more upcoming targeted therapies and she drove clinical and basic research in the field of PH to strive for optimal patient care. Moreover, she has been a passionate medical professional and a true friend to many of us. Therefore, we would like to dedicate this special series to her memory ([Appendix 1](#)).

The series starts with a commentary from Lammers and Aplitz on the new PH definition and its impact on pediatric PH. According to international guidelines, PH used to be defined as elevation of the mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg. During the 6th World Symposium on PH in 2018, a revised hemodynamic definition of PH was proposed, lowering the threshold from ≥ 25 mmHg to >20 mmHg (2). This new definition has also been accepted by the Pediatric Task Force of the World Symposium to establish a uniform language and facilitate transition to adult services (3). This decision resulted in controversial debates within the expert community as the new definition may lead to overdiagnosis and overtreatment of PH. Therefore, a critical expert discussion on the impact of the new PH definition in pediatric PH is provided (4).

While the definition of PH is still based on invasive hemodynamic measures, assessment of cardiopulmonary hemodynamics by cardiac catheterization and acute vasoreactivity testing (AVT) in the catheterization laboratory is critical and remains the gold standard for the diagnosis of PH. Invasive assessment of PH has to be performed in the context of the patient's age, medical history, and functional status. A systematic catheterization protocol is needed and has been established for pediatric PH by Kaestner *et al.* (5)

While we know that patients with vasoreactive PAH have a better prognosis, the question “how do we define vasoreactivity” is still an ongoing matter of debate. The study of Aplitz *et al.* adds new insights into this topic and helps to understand the clinical implications of positive response during vasoreactivity testing (6). They also evaluated the clinical and prognostic value of the diastolic PA pressure (dPAP) compared to mPAP. The authors conducted a retrospective analysis of the international TOPP (Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension) registry and evaluated hemodynamic data of 246 children with IPAH/HPAH. They compared the correlation between dPAP and mPAP, as well as hemodynamically-derived calculations (PAP/SAP, PVRI, TPG), using both dPAP and mPAP, at rest and during acute vasoreactivity testing (AVT) in children with idiopathic or heritable PAH. In addition, they assessed the association of these metrics (at baseline and changes after AVT) with transplant-free survival.

Mostly, the first diagnostic tool and modality in suspected PH is the transthoracic echocardiogram. Echocardiography does not only allow a comprehensive initial assessment of cardiac anatomy, dimensions and function of both ventricles, it may also confirm the suspicion of elevated pulmonary pressures and may allow for the estimation of prognosis. Lammers *et al.* provide

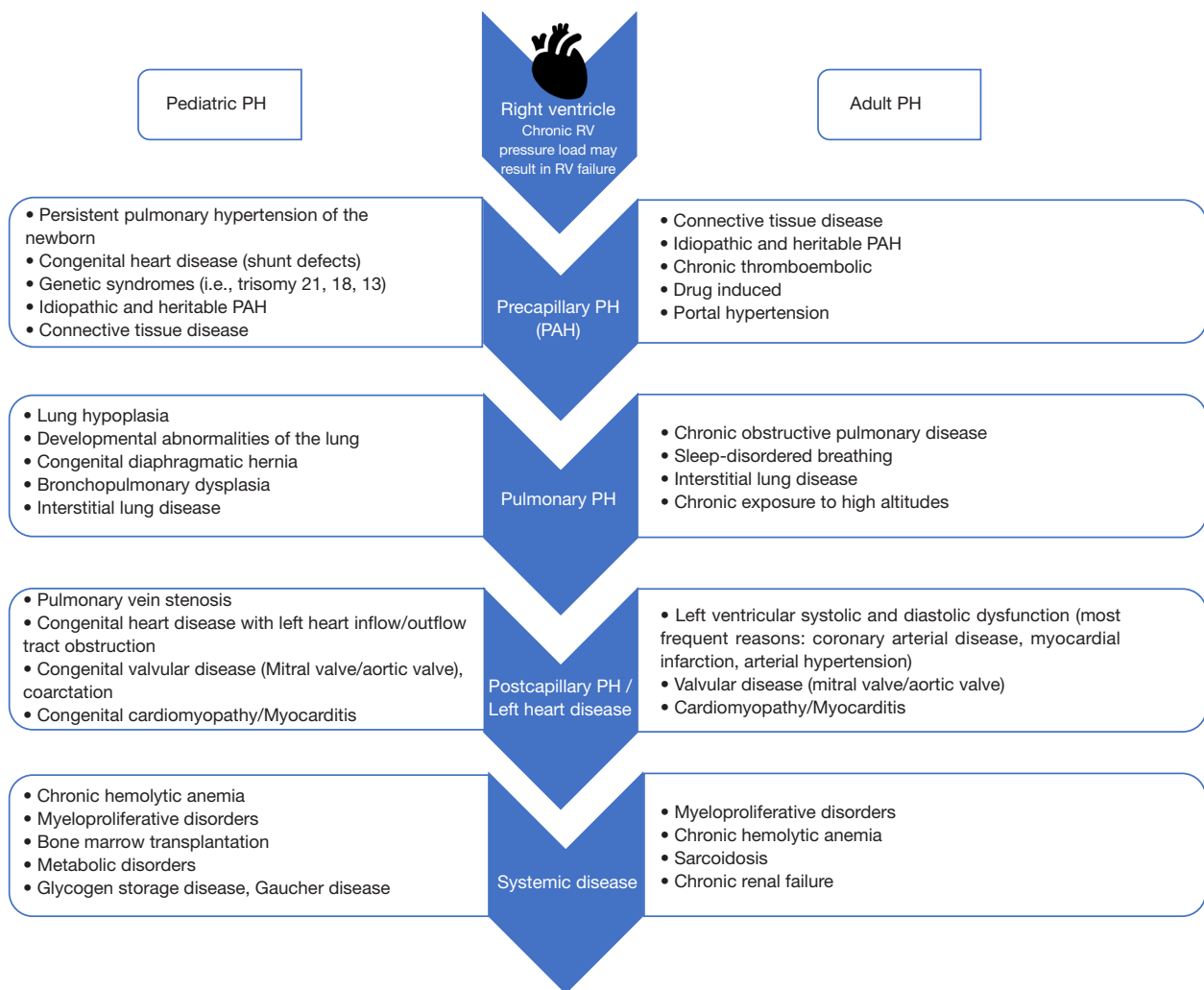


Figure 1 Similarities and differences in the etiology of pediatric and adult pulmonary hypertension.

a practical approach and a concise and clinically applicable echocardiographic guidance and present basic variables, which should be obtained at any assessment (7). Moreover, they present additional advanced echocardiographic measures, that can be applied in a research or clinical setting.

A very comprehensive assessment of the RV and the pulmonary vasculature is nowadays possible by cardiac magnetic resonance (CMR). This technique has become an essential non-invasive imaging modality in the management of PH. Latus and Meierhofer provide many insights in its usefulness in pediatric PH and discuss the clinical relevance of advanced MR parameters (8).

Beyond clinical and functional assessment, as well as imaging examinations, follow-up care of patients with PH usually includes the measurement of biomarkers. In the meantime, many biomarkers have shown important prognostic impact in children with PH, as excellently summarized by Ploegstra and Berger (9).

During the past few years, treatment of PAH has undergone a remarkable evolution. Due to the complex etiology and relative lack of data in children with PAH, appropriate therapies have to be selected after careful and comprehensive review of a PH expert referral center according to current international recommendations. However, in pediatric PAH also specific pharmacokinetic aspects have to be considered and were presented in detail by Gorenflo and Ziesnitz (10).

Perhaps the most innovative approach in pediatric PH in the last decade was the renaissance of the Potts shunt as a procedure to treat children with severe PAH and systemic or suprasystemic RV pressures and imminent RV failure. Schranz

et al. present in this series an impressive pathophysiological view on new interventional and surgical approaches to treat children with PH and heart failure (11).

Lung transplantation is a treatment option for selected children with end-stage PH, which is the second most frequent indication for children requiring a lung transplantation. Sommer and Warnecke describe in detail challenges of specific considerations in children with PH regarding criteria for listing to lung transplantation, allocation policies, bridging strategies with extracorporeal support, and perioperative management (12). Bilateral lung transplantation using cardiopulmonary bypass to provide hemodynamic stability is nowadays the standard surgical approach in pediatric centers. Warnecke *et al.* also provide current data on long-term survival from the largest and most experienced pediatric lung transplant center in Germany.

The Eisenmenger syndrome is regarded as the most advanced form of PAH associated with congenital heart disease. There have been many insights for the treatment of Eisenmenger patients in the last decade, helping to improve outcome of these patients. Diller *et al.* provide a comprehensive overview on these developments and future prospects (13).

The Fontan circulation is a palliative concept for patients with univentricular hearts. The central veins are directly connected to the pulmonary arteries (cavo-pulmonary connection) to separate the pulmonary and the systemic circulation. Pulmonary blood flow is determined by central venous pressure and pulmonary vascular resistance. Therefore, systemic ventricular preload and cardiac output are dependent on a healthy lung with low pulmonary vascular resistance.

While pulmonary vascular disease and increased pulmonary resistance may result in Fontan failure, these considerations support the use of pulmonary vasodilators. The review of Becker *et al.* summarizes the current knowledge of the effects and efficacy of pulmonary vasodilator therapy in Fontan patients (14).

At an altitude of about 2,500 m, the barometric environmental pressure is reduced and the partial pressure of inspired oxygen drops from 21% to 15% (hypobaric hypoxia). Therefore, children with PH may be at risk during high-altitude exposure, by air travel or recreational activities, such as hiking and skiing. Little is known about the physiological response and risk of developing clinically relevant events on altitude exposure in pediatric PH. The review article of Herberg *et al.* summarizes the current clinical knowledge on moderate to high altitude exposure in patients with different forms of pediatric PH (15).

PAH is often associated with cardiac autonomic dysfunction, and heart rate variability (HRV) as marker of cardiac autonomic function is related to disease severity. Knowledge about the effects of physical activity on HRV is limited in PAH patients. Siaplaouras *et al.* assessed in their study whether HRV parameters can be influenced by a homebased exercise training program and whether respective changes are related to levels of activity (16). In their pilot study they were able to demonstrate that a workout program of 16 weeks revealed an activity level dependent effect on parameters of autonomic cardiac function in children and adolescents with PAH. This mechanism might contribute to the positive effects of exercise training in patients with PAH.

In this special series, we also report on rare etiologies of PH in children:

While in adult patients, PAH associated with connective tissue disease (CTD-PAH), including systemic sclerosis (SSc), is the most commonly identified type of disease-associated PAH, this PAH subtype is much more rarely in children. Apitz and Girschick present in their review article recent findings on diagnosis and therapy of SSc-associated PAH in children (17). Since SSc-PAH is complex and difficult to diagnose, as symptoms are non-specific and may be complicated by other diseases such as interstitial lung disease or left heart disease, regular screening for early detection of PAH is critical in pediatric SSc patients in order to improve patient outcomes.

Pulmonary veno-occlusive disease (PVOD) is a rare disease leading to PH and potentially death related to right heart failure and/or respiratory insufficiency. Clinical symptoms are heterogenous and nonspecific. Pfluger and Humpl provide an overview on current evidence on this rare disease (18). They state that lung transplantation is currently the only valid treatment option for patients with PVOD.

Moyamoya disease (MD) is a rare vaso-occlusive disorder that primarily affects intracranial cerebral arteries. The involvement of extracranial vessels is unusual. However, there are previous reports suggesting MD to be a systemic disorder, causing disease manifestations in vessels of other parts of the body. Krämer *et al.* provide a case presentation demonstrating that pulmonary arterial hypertension is a rare comorbidity in patients with MD, especially in patients with genetic predictors such as the RNF213 mutation (19). They recommend regular echocardiographic screening for early signs of PAH in patients with MD for early detection and treatment.

By bringing together a number of specialists to refine and advance current knowledge on the topic of pediatric PH, we hope

that this special series may stimulate and inspire physicians and researchers in order to move forward with care of children with this progressive and complex disease, true to the motto “It’s through collaboration that advances are made.”

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Sheila Glennis Haworth CBE

A tribute to a pioneer in the fight against pulmonary hypertension

Sadly Sheila Glennis Haworth, who had dedicated her professional life to academic and clinical research into pulmonary hypertension, died aged 81 at her home in Oxfordshire after a short illness in October 2020.

We were delighted and honoured when she accepted the invitation to give the opening lecture on “Lung development and pathogenesis of pulmonary vascular disease” at our Münster Symposium in 2019.

Her early medical career started at the Royal Free Hospital followed by paediatric training at Queen Elizabeth Hospital for Children. She also worked as a fellow at the Presbyterian & Babies Hospital, Columbia University in New York. She began her clinical career as a junior doctor at the Hammersmith Hospital and Great Ormond Street Hospital for Children, during which time she developed her passion for academic work. She participated in the Paediatric Developmental Biology and Pathology Initiative at the Department of Experimental Pathology at the Cardiothoracic Institute at the Royal Brompton Hospital where she was mentored by Professor Lynn Reid.

Professor Haworth worked on the developmental vascular pathology of congenital heart disease, as well as pre- and postnatal modulation of vascular growth and function, which had been the topic of her MD thesis. This helped her gain deep insight into the pathophysiology of pulmonary vascular disease.

She was appointed an Honorary Paediatric Consultant in 1977 and was promoted to the Chair of Developmental Cardiology at the Institute of Child Health in 1988. In 1990 the British Heart Foundation agreed to fund the Chair, and Professor Haworth became the first female to have been so honoured. She founded the UK Paediatric Pulmonary Hypertension Service in 2002 with a nationwide network and satellite centres all over the UK - an outstanding example of collaborative clinical networking. She became Emeritus Professor in 2004 but continued to work for the Pulmonary Hypertension Service and was academically active until her untimely death. Professor Haworth one of the founder members of the Pulmonary Vascular Research Institute (PVRI) in 2004 and was the first Paediatric Taskforce Leader. She was elected President of the Institute in the years 2014–2016. She contributed to its successful expansion and actively shaped the structure of the PVRI. She played a key role, setting up a link with the Indian subcontinent on behalf of the PVRI, and in establishing clinical and scientific networks around the world. She was a true pioneer who took part in the last few years with more targeted therapies, and she drove clinical and basic research in the fields of pulmonary hypertension and collaborative networking to strive for optimal patient care.

For her outstanding distinguished work and service to cardiology in the NHS and recognizing her foundation role in setting up the UK Paediatric Pulmonary Hypertension Service, she was made a Commander of the Most Excellent Order of the British Empire (CBE) receiving her award from Her Majesty the Queen in 2007.

Glennis, as she was known by her family and widely within the profession, was a highly respected academic and clinical scientist and a medical professional of international standing. She was passionately dedicated to her work, committed to striving for excellence and always showing sincere empathy for her patients and fellows. She was a role model in every way and adored by the many people who were fortunate in getting to know her. She had a great sense of humour and enjoyed painting, playing the piano, opera and travelling.

She is not only greatly missed by her husband, Major General Leslie Busk, who was the Director General of the British Heart Foundation from 1990–2004, and her family, but also by the many friends and colleagues all over the world, for whom she had been a true friend and role model.

We would like to dedicate this Special edition to her memory.



Sheila Glennis Haworth, CBE

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