Review Article

# Pulmonary vascular disease as a complication of pediatric congenital heart diseases

**Julie Wacker[1,2,3]^, Raphael Joye[1,2,3]^, Leon Genecand[2,4]^, Frederic Lador[2,4]^, Maurice Beghetti[1,2,3]^**

[1]Pediatric Cardiology Unit, Department of Pediatrics, Gynecology, and Obstetrics, Geneva University Hospitals, Geneva, Switzerland; [2]Pulmonary Hypertension Program, Geneva University Hospitals, Geneva, Switzerland; [3]Centre Universitaire Romand de Cardiologie et Chirurgie Cardiaque Pédiatrique (CURCCCP), University of Geneva, Geneva, Switzerland; [4]Division of Pulmonary Medicine, Department of Medicine, Geneva University Hospitals, Geneva, Switzerland

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*Correspondence to:* Julie Wacker, MD. Pediatric Cardiology Unit, Department of Pediatrics, Gynecology, and Obstetrics, Geneva University Hospitals, Rue Willy Donzé 6, 1211 Geneva, Switzerland. Email: julie.wacker@hcuge.ch.

**Abstract:** Congenital and acquired heart diseases can cause pulmonary hypertension (PH) in children, either by increasing pulmonary blood flow (PBF), left atrial pressure (LAp), and/or pulmonary vascular resistance (PVR). Pathophysiological process of pulmonary vascular disease (PVD) in different types of congenital heart diseases (CHDs) are reviewed hereafter. As with other types of PH, a rigorous diagnostic evaluation is mandatory to characterize the etiology of the PH, rule out other or additional causes of PH, and establish a risk profile. Cardiac catheterization remains the gold standard exam for PH diagnosis. Treatment of pulmonary arterial hypertension (PAH) associated with CHD (PAH-CHD) can then be started according to the recent guidelines recommendations, although most of the evidence is extrapolated from studies on other causes of PAH. PH in pediatric heart disease is often multifactorial, and sometimes unclassifiable, making the management of these patients complicated. The operability of patients with a prevalent left-to-right shunt and increase of PVR, the management of children with PH associated with left-sided heart disease, the challenges of pulmonary vascular disorders in children with univentricular heart physiology and the role of vasodilator therapy in failing Fontan patients are some of the hot topics discussed in this review.

**Keywords:** Pulmonary hypertension (PH); congenital heart disease (CHD); Eisenmenger syndrome; Fontan; pulmonary vascular disease (PVD)

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## Introduction

Pulmonary hypertension (PH) is a serious disease with a poor prognosis, progressing without treatment to right heart failure and death. Two main etiologies of pediatric PH are idiopathic pulmonary arterial hypertension (iPAH), and PAH associated with congenital heart disease (PAH-CHD) (1). This last condition encompasses mainly CHD with a systemic to pulmonary shunt, and are classified in World Health Organization (WHO) classification group 1, among other causes of PAH (*Table 1*). However, other congenital or acquired heart diseases can cause distinct types of PH, like mitral stenosis, Shone complex, or cardiomyopathy classified

^ ORCID: Julie Wacker, 0000-0001-5408-1107; Raphael Joye, 0000-0002-2201-0096; Leon Genecand, 0000-0001-6965-0480; Frederic Lador, 0000-0002-4276-635X; Maurice Beghetti, 0000-0002-1841-0927.

**Table 1** Clinical classification of PH, and clinical classification of PAH-CHD

| |
|---|
| Group 1 PAH |
| 1.1 Idiopathic PAH |
| 1.2 Heritable PAH |
| 1.3 Associated with drugs and toxins |
| 1.4 Associated with |
| 1.4.1 Connective tissue disease |
| 1.4.2 HIV infection |
| 1.4.3 Portal hypertension |
| 1.4.4 CHD |
| Systemic-to-pulmonary shunt lesions: |
| A. Eisenmenger's syndrome |
| B. PAH associated with prevalent systemic to pulmonary shunt |
| C. PAH with small/coincidental defects |
| D. PAH after defect correction |
| 1.4.5 Schistosomiasis |
| 1.5 PVOD/PCH involvement |
| 1.6 Persistent PH of the newborn syndrome |
| Group 2 PH associated with LHD |
| 2.1 Heart failure |
| 2.1.1 with preserved ejection fraction |
| 2.1.2 with reduced or mildly reduced ejection fraction |
| 2.2 Valvular heart disease |
| 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH |
| Group 3 PH associated with lung diseases and/or hypoxia |
| 3.1 Obstructive lung disease or emphysema |
| 3.2 Restrictive lung disease |
| 3.3 Lung disease with mixed restrictive/obstructive pattern |
| 3.4 Hypoventilation syndrome |
| 3.5 Hypoxia without lung disease (e.g., high altitude) |
| 3.6 Developmental lung disorders |
| Group 4 PH associated with pulmonary artery obstructions |
| 4.1 Chronic thrombo-embolic PH |
| 4.2 Other pulmonary artery obstructions |
| Group 5 PH with unclear and/or multifactorial mechanisms |
| 5.1 Hematological disorders |
| 5.2 Systemic disorders |
| 5.3 Metabolic disorders |
| 5.4 Chronic renal failure with or without hemodialysis |
| 5.5 Pulmonary tumor thrombotic microangiopathy |
| 5.6 Fibrosing mediastinitis |

PH, pulmonary hypertension; PAH-CHD, PAH associated with CHD; PAH, pulmonary arterial hypertension; CHD, congenital heart disease; HIV, human immunodeficiency virus; PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary hemangiomatosis; LHD, left heart disease.

in the second group of the classification, PH due to left heart disease (PH-LHD). Lastly, pulmonary vascular disease (PVD) in the univentricular palliation of complex CHD can lead to failure of the Glenn or the Fontan circulation. Although not a PH as per the definition, this entity is increasingly recognized although not yet really addressed in the European PH guidelines (2). Of note, with the improved survival of children with CHD, PAH-CHD is an ever growing population of adult PAH, contributing to increased morbidity and mortality. According to French and Scottish registries, prevalence of PH in adults with CHD reaches 1.6 to 12.5 cases per million (3,4).

PVD in PAH-CHD is a multifactorial process, incompletely understood, involving inflammation, auto-immunity, vasoconstriction, cellular proliferation and *in situ* thrombosis (5,6). The risk of developing PH depends on hemodynamic factors (for example the location of the defect, its size, and the magnitude of the shunt), the age of the patient, the presence of potential comorbidities, and a possible genetic susceptibility (7).

Early corrective surgery of congenital shunts prevents advanced pulmonary vascular lesions from developing in the vast majority of cases. In countries with limited health resources, timely surgery is not always achievable, and children with left to right shunts can present with end-stage PVD, called the Eisenmenger syndrome, when pulmonary vascular resistance (PVR) exceeds systemic vascular resistance, leading to shunt reversal and cyanosis. Moreover, and all over the world, Eisenmenger syndrome can also occur because of diagnosis delay. According to epidemiological estimates,

over three millions of children around the world are at risk of developing Eisenmenger syndrome (8). Management of Eisenmenger syndrome will be reviewed in detail.

The management of children with moderate increase of without the PVR is controversial, without evidence-based hemodynamic criteria to discriminate between the operable and the inoperable patient. We will review the data available for this group of patients and discuss their operability.

Managing children with PAH remains a challenge due to the lack of randomized controlled trials (RCTs) on the efficacy of pulmonary vasodilators in pediatrics. Treatment is based on international expert recommendations, data extrapolation from adult studies, and small-scale pediatric studies. Targeted therapies can slow clinical deterioration in different types of pediatric PAH, but curative treatment remains elusive.

In this article, we review the complex relationship between CHD, PH, and PVD, comment on the classification of PAH-CHD, and discuss diagnosis strategy and treatment of PH in children with CHD.

## Definition and classification

PH definition has been revised at the 6th World Symposium on PH (WSPH) in Nice (France) in 2018: PH is now defined by a mean pulmonary artery pressure (mPAP) >20 mmHg at rest measured by right heart catheterization (9). Moreover, a PVR >2 wood units (WU) or indexed PVR (PVRi) ≥3 WU·m$^2$ in children, is used to assess the presence of PVD (10).

Of note, available literature is based on previous guidelines with PH defined as a mPAP ≥25 mmHg (11). It is unclear how this recent change of cut-off value will impact the field of PAH-CHD.

The WHO PH classification has undergone multiple revisions, reflecting the evolving understanding of the disease. The latest version of the WHO classification is summarized in *Table 1*, with a focus on the categories of interest for pediatric PH associated with diverse types of CHD.

An intent has been made in 2011 to develop a classification more specific to PH in childhood. This Panama classification is however less used clinically, in the literature and in the guidelines (12).

## PAH-CHD

### *Definition*

PAH-CHD is a heterogenous population that is defined by the combination of PH, the presence of a CHD, and the exclusion of a post-capillary PH (PH group 2). The name PH-CHD can be misleading, as this category only includes patients with a shunt between the systemic and the pulmonary circulation.

### *Pathophysiology*

Pressure in the pulmonary artery is determined by the pulmonary blood flow (PBF) times the PVR, according to the equation $\Delta p = PBF \times PVR$. The $\Delta p$ in the pulmonary vascular bed is the mPAP minus the left atrial pressure (LAp), also referred to as the transpulmonary gradient (TPG). Simplifying the equation, we obtain: $mPAP = PBF \times PVR + LAp$. This highlights that pressure increase in the pulmonary artery can be due to an increase in PBF, PVR, or LAp, but sometimes to a combination of the three parameters, making the classification of CHD sometimes complex (7).

Despite the tremendous progress in medical research in this field, the mechanisms that underlie the development of PAH in patients with CHD are still not completely understood. If initially the raised pulmonary arterial pressure in PAH-CHD is due to increased PBF, PVR will progressively increase as the PVD develops. Increased PBF initially leads to flow-mediated dilatation of the pulmonary arterioles, with no or minimal increase of PAP. However, after long-standing increased PBF, flow-mediated vascular injury will lead to increased PVR (13). Several phenomena contribute to the raise in PVR, including vasoconstriction, vascular proliferation, remodeling of the arteriolar wall, and thrombotic events. The trigger for PVD development has not been identified, but shear stress modification is thought to lead to endothelial dysfunction, with a consecutive imbalance in vasodilator/anti-proliferative and vasoconstrictive/mitogenic mediator production and thrombogenic and inflammatory factors production. A pre-tricuspid shunt, like an atrial septal defect, with consecutive increased PBF but without transmission of the systemic pressure into the pulmonary artery will cause much less damages on the lung vasculature than a post-tricuspid shunt, like a ventricular septal defect (VSD), because the pulmonary circulation is not efficient at normalizing shear stress with increased flow and high pressure (13).

Histologically, vascular remodeling involves the three layers of the arteriolar wall: Proliferation of endothelial cells and fibrosis occur in the intima and is accompanied by medial hypertrophy as well as deposition of collagen

and elastin in the extracellular matrix and adventitia. Moreover, smooth muscle cells extend into peripheral arteries (6). Porcine and ovine models of shunt-associated PAH have been studied, showing the aforementioned pulmonary vascular lesions, in an inhomogeneous manner, confirming the patchy distribution of the lesions, and could offer further understanding of the mechanisms leading to vascular pathology in PAH-CHD (14,15).

Apoptosis resistance phenomenon have been hypothesized in the pathogenesis of PAH-CHD. The correlation between apoptosis resistance of the endothelial cells [showing anti-apoptotic protein B cell lymphoma protein-2 (Bcl-2)], intimal proliferation and PAH irreversibility opens new perspectives in the management of pre-Eisenmenger patients (16).

Hemodynamic factors cannot fully explain the inter-individual variability of PAH development in CHD. A permissive genetic trait could confer particular susceptibility to PVD development. However, mutations in genes responsible for familial forms of PAH like bone morphogenetic protein receptor 2 (*BMPR2*), activin-like receptor kinase-1 (*ALK-1*), endoglin (*ENG*), mothers against decapentaplegic 9 (*SMAD9*) have been detected only in a minority of patients in PAH-CHD (17). Other mutations, including those identified more recently in other subsets of PH, like T-box transcription factor 4 (*TBX4*) and SRY-box transcription factor 17 (*SOX17*), may play a role in the pathophysiology of PAH-CHD and help explain individual susceptibility (18-20).

In children with CHD, comorbidities including chromosomal defects and developmental lung disease can contribute to PH development. Down syndrome has been reported in as much as 11% of children with PH in different registries (21,22). Patient with trisomy 21 are at risk of developing PH because of associated CHD, but also because of various vascular, parenchymal, ventilatory and developmental respiratory complications. Developmental lung disease, including bronchopulmonary dysplasia in preterm children and congenital diaphragmatic hernia, are comorbidities that need to be considered in infant.

### *Classification*

Four distinct phenotypes of PAH-CHD have been delineated in the international guidelines differing in terms of management strategies and treatment response (*Table 1*).

The first subgroup includes patients with Eisenmenger's syndrome, at the final and irreversible stage of PAH-CHD. These patients are increasingly included in drug trials, and benefit from targeted treatments, i.e., specific pulmonary vasodilators. The second group encompasses patients with PAH associated with a prevalent systemic-to-pulmonary shunt, at an earlier stage of the disease. This is a heterogeneous group, with moderate to large defects and mildly to moderately increased PVR. Some patients are considered operable whereas a fraction of them is considered inoperable, on controversial criteria. Contrary to Eisenmenger's syndrome patients, these patients are rarely included in clinical trials, and their management is a challenge. The third group comprises patients with a small/coincidental defect that is not believed to be the cause of PAH. These patients behave similarly to idiopathic PAH patients and closure of the defect is contra-indicated. Finally, the last group is constituted by patients with a persisting or recurrent PAH after CHD correction. Their poor prognosis underlines the need to establish better operability criteria (23). Of note, because some congenital cardiac surgeries can lead to valvular stenosis or insufficiency, ruling out any residual anatomical issue that could affect hemodynamics and provoke post-capillary PH is necessary. This classification of PAH-CHD has some limitations for children with as much as 11% of pediatric patients with CHD and PH that could not be attributed to any of the four subgroups (24).

### *Diagnosis and risk assessment*

Patients with a shunt should undergo a thorough diagnostic work-up, including history, clinical examination with blood oxygen saturation, chest X-ray and echocardiography (25). Other or additional causes of PH need to be ruled out. Eisenmenger syndrome and coincidental defects can be diagnosed based on this evaluation, even if further investigations, including right heart catheterization, are performed for PAH-CHD diagnostic confirmation, and risk assessment. Right heart catheterization with pulmonary arterial wedge pressure measurement, or concomitant left heart catheterization gives also valuable information regarding a potential postcapillary component in longstanding CHD.

Patients with a prevalent systemic-to-pulmonary shunt require further investigations, in order to decide operability, if some features of PAH are present. PAH should be suspected in patients with late presentation, absence of pulmonary congestion, absence of failure to thrive, presence of associated syndromes or comorbidities suggesting genetic disorders, post-tricuspid localization of the shunt,

bidirectional shunting, systemic oxygen desaturation, and the presence of complex anomalies (especially those involving obstruction to pulmonary venous flow) (26). In those patients, additional non-invasive workup may be considered in selected cases, including oxygen saturation on exercise [arm and leg in the setting of a patent ductus arteriosus (PDA)], chest computed tomography (CT) to rule out parenchymal lung disease, and cardiac magnetic resonance imaging (MRI) or nuclear perfusion scan for pulmonary-to-systemic flow ratio (Qp:Qs) estimation. Moreover, cardiac catheterization should be performed, allowing to obtain pressure measurement, and PVR estimation. Indeed, PVR is calculated using measured pressures, and cardiac output based on the Fick principle. To allow the best estimation of PVR for these patients, it is mandatory to use direct Fick with the measurement of oxygen consumption (2). However, few catheterization laboratories have the material for the measurement of oxygen consumption, and they rely on estimated oxygen consumption to assess cardiac output with the indirect Fick method, which is an important source of bias. Indeed, indirect Fick has been demonstrated to have poor precision and is no more recommended by the international guidelines (2,27). Different studies and task forces have suggested operability cut-off values based on hemodynamic criteria obtained during right heart catheterization. The pediatric task force of the 6$^{th}$ WSPH issued a table with very conservative operability criteria: patients with a PVRi <4 WU·m$^2$ are consensually deemed operable, and the expected outcome is a reduction or normalization of the pulmonary arterial pressure with defect closure. Patients with a PVRi >8 WU·m$^2$ are considered inoperable. In between these two extremes, operability should be decided on an individual basis, taking into account the age of the patient, the type of defect, any comorbidities, and baseline and exercise saturation (10).

Slightly different hemodynamic criteria have been issued by the European Pediatric Pulmonary Vascular Disease Network and the American Heart Association: shunt closure should be considered if PVRi <6 WU·m$^2$, or ratio of PVR: systemic vascular resistance <0.3 at baseline. Acute vasoreactivity testing should help determine operability for patients with elevated baseline PVRi (28,29).

However, none of these values have been validated in prospective studies, and therefore cannot represent strong guidelines. As the authors of the pediatric task force of the 6$^{th}$ WSPH pointed out, hemodynamic criteria should be interpreted as general guidance for assessing operability in PAH-CHD, keeping in mind that "*the long-term impact of defect closure in the presence of PAH with increased PVR is unknown*" (10).

Operability (surviving shunt closure) does not mean reversibility of PH (normalizing hemodynamics and regression of the pulmonary vascular lesions) (30). Hemodynamics have been shown to be a poor predictor of reversibility, and therefore an unsuitable surrogate marker for long-term outcome. There is a need to find criteria able to better discriminate patients who will benefit from shunt closure with reversal of PAH.

Identifying patients who will normalize their hemodynamics after shunt closure is of paramount importance. Indeed, the poor prognosis of persisting PAH after shunt closure compared to other groups of PAH-CHD has been demonstrated (23,31).

In adults, exercise testing is part of the diagnostic workup of PH, possibly orientating on the PH etiology, assessing functional capacity and exercise limitation, and contributing to risk stratification (2). In children, when feasible (usually not before 6 years old), exercise testing may identify characteristic features of exercise limitation due to PVD, such as high ventilatory equivalent for carbon dioxide ($VE/VCO_2$) slope, a low end-tidal partial pressure of carbon dioxide ($PETCO_2$), and low peak oxygen uptake ($VO_2$), and help in functional class assessment (10). However, pediatric reference values for cardiopulmonary exercise testing and association with outcome are lacking. Six-minute walk test is more widely performed in children, and contributes to risk stratification, although not reliable in young children (under 6 years old). In patients with PAH-CHD, oxygen saturation during exercise is an important measure. A drop of oxygen saturation indicates a right to left shunting (32).

### *Treatment*

General measures recommended for pediatric patients with PAH apply to PAH-CHD. Immunizations should be up to date [especially influenza, pneumococcal and coronavirus disease 2019 (COVID-19)]. Dehydration should be avoided, and moderate physical activity should be encouraged. Diuretics are indicated when right heart failure and fluid retention develop. Oxygen therapy may be considered in patients with severe hypoxemia at rest or during exercise. Anticoagulation is of unclear benefit, and usually reserved for patients on prostacyclin analogues infusion, because of the additional risk of catheter-associated thrombosis. Iron deficiency should be substituted, considering the risk of

 

adverse outcome (33).

The three main pathophysiological pathways currently known to be implicated in the pathogenesis of PAH [endothelin, nitric oxide (NO), and prostacyclin] are the targets of specific PAH therapies (34). Endothelin receptor antagonists (ERAs) (bosentan, macitentan, ambrisentan), phosphodiesterase type 5 (PDE-5) inhibitors and guanylate cyclase stimulators (sildenadil, tadalafil, riociguat), prostacyclin analogues and prostacyclin receptor agonists (epoprostenol, treprostinil, selexipag) are all used commonly in Eisenmenger syndrome despite limited evidence. We will not enter in too much details on existing data for the use of each pulmonary vasodilator in PAH-CHD, as other recent reviews have exhaustively detailed the published studies results (35). Of note, the majority of pulmonary vasodilators are used off-label in children, because of the lack of large scale clinical studies and the difficulty to design and conduct RCT in the pediatric PH population (36).

Looking back at the clinical classification table, pulmonary vasodilators are used in Eisenmenger syndrome, PAH with small/coincidental defects and PAH after defect correction. Treatment of PAH associated with prevalent systemic-to-pulmonary shunts depends on the diagnostic evaluation. In operable patients, closure of the shunt is performed. In inoperable patients, various treatment strategies are used, including an expectative strategy and treatment once the shunt has clearly reversed, or treat with pulmonary vasodilators, which can worsen the situation if the left-to-right shunting remains prevalent. Treatment can be used as an "intent to repair", although this would constitute high risk surgery, probably with patch fenestration, a strategy that appears in the guidelines, but lack any evidence (29). Indeed, the cases reported in the literature are mainly patients with a pretricuspid shunt, which may not have been the cause of the PAH in the first place (37). The "repair and treat" method is discouraged considering the poor prognosis of PAH after defect correction.

Treatment strategy for PAH has moved towards upfront combination therapy rather than sequential association, in order to achieve a better control of the disease (38-40). However, this strategy lacks evidence in Eisenmenger patients, and the recent guidelines state that "*combination drug therapy may be considered in patients with Eisenmenger syndrome*", with a class of recommendation IIb (2). Data from the TOPP international registry show that the majority of children are still started on monotherapy (41).

The ultimate palliation for PH is lung transplantation, associated with corrective cardiac surgery in the case of PAH-CHD, or combined heart and lung transplantation. However, shortage of organ donors, waitlist mortality and survival prospect in children following lung transplantation have limited the long-term success of this procedure (42). Atrial septostomy or reverse Potts shunt are increasingly performed to delay the need for lung transplantation but are usually unnecessary for children with Eisenmenger syndrome, as a shunt with reverse flow already exists by definition.

Targeted therapies improve quality of life, slow disease progression and possibly reduce mortality (43). However, curative therapy remains elusive. PAH prevention in patients with left-to-right shunts is paramount. Prevention can take various forms, from antenatal diagnosis of CHD, to early pediatric cardiology referral and early surgical correction. For example, VSD and PDA are typically closed before the age of 6 to12 months, atrioventricular septal defect at 3 to 6 months, and truncus arteriosus before 3 months of age (44).

Some specific clinical situations need to be considered outside of these general categories. Infants with PH, developmental lung disorder and a left-to-right shunt (most frequently a PDA) represent an ever-growing population due to improved survival of extreme preterm babies. It is assumed that a PDA can contribute to the development of bronchopulmonary dysplasia by increasing PBF, leading to lung injury and inflammation. Hemodynamically significant shunts should hence be closed without delay in these patients. Standardization of the definition of hemodynamically significant PDA is however lacking (45).

## PH-LHD

### *Pathophysiology*

PH-LHD constitute group 2 of PH classification. Congenital post-capillary obstructive lesions (e.g., pulmonary vein stenosis, cor triatriatum, obstructed total anomalous pulmonary venous return, mitral or aortic stenosis, coarctation of the aorta) is a subgroup of this category of interest in pediatrics. Most of the adults in group 2 have some degree of heart failure with preserved or reduced ejection fraction or valvar heart disease. If some pediatric patients also exhibit similar acquired LHD, especially patients with rheumatic heart diseases or cardiomyopathies, extrapolation from adult studies may not be applicable in children born with left sided heart

disease since the disease is present in utero and can affect pulmonary vascular development (46).

A recent international survey on the pre heart transplant management of PH-LHD in children revealed a significant heterogeneity in practices among recognized expert centers (47).

PH-LHD is currently defined by a mPAP >20 mmHg with a pulmonary artery wedge pressure (PAWP) >15 mmHg. There is however a distinction between isolated post-capillary PH (IpcPH), where the PVR ≤2 WU (or PVRi <3 WU·m$^2$), and combined pre- and post-capillary PH (CpcPH) where PVR >2 WU (or PVRi ≥3 WU·m$^2$).

In IpcPH, increased LA pressure is transmitted passively to the postcapillary venous network and the pulmonary artery bed. In CpcPH, comprising as much as 20% of patients with PH-LHD, there is first a reflex vasoconstriction of the pulmonary veins and/or arteries following activation of stretch receptors located in LA and pulmonary veins. Moreover, endothelial dysfunction and remodeling of the pulmonary arteries and veins can occur, different from the plexiform lesions of long-standing left-to-right shunts, leading to PVD (48).

### *Treatment*

Treatment of the underlying LHD is the mainstay of PH-LHD management. In most cases, reversibility or improvement of PH after successful causal treatment can be expected (49-51). Nevertheless, the historical conception that PH-LHD is reversible has been challenged by the observation that some patients display residual PH even after successful reduction of LAp (52). Precise hemodynamic values before and after intervention could contribute to identify patients at increased risk of residual PH.

The majority of studies on pulmonary vasodilators in PH-LHD have failed to show a clear benefice (53-57), or even reported a clinical deterioration (58-60). The potential deleterious effect of pulmonary vasodilation in patients with left sided heart failure, leading to increased pulmonary venous congestion and worsening clinical scenario could explain those discouraging results.

The use of pulmonary vasodilators is appealing in the category of patients with CpcPH, although not currently recommended due to lack of evidence. RCT including those patients specifically are needed.

## PVD in the univentricular heart palliation

### *Pathophysiology*

The Fontan procedure, or total cavopulmonary anastomosis, is the ultimate surgical step of single ventricle palliation. Systemic venous return bypass the heart and flows passively into the pulmonary arteries, whereas the single ventricle pumps oxygenated blood into the systemic circulation. Before the Fontan operation, usually completed at the age of 4 years, one or two surgical steps are necessary. First, depending on the underlying anatomy and native PBF, a pulmonary artery band or a systemic to pulmonary shunt is required in the first weeks of life (with atrioseptectomy and extensive aorta reconstruction whenever necessary). Then, at around 4 to 6 months of age, a superior cavopulmonary anastomosis (Glenn procedure) is performed.

Without a subpulmonary ventricle, PVR and PAP play a crucial role in regulating PBF, and even low grade of PVD can impact prognosis (9). However, children with single-ventricle CHD often have comorbidities or risk factors for abnormal pulmonary vascular bed: genetic syndrome, abnormal lung development, and abnormal PBF in the early months of life with systemic-to-pulmonary shunts (too much, exposing the lung vasculature to detrimental high flow and pressure; not enough, leading to restricted growth of the pulmonary arteries and vascular bed, with a future risk of decreased capacitance and increased PVR; or maldistributed, causing patchy pulmonary hypoplasia or varying degrees of vascular disease). The Glenn circulation in itself generates an abnormal environment for the pulmonary vascular bed, with diminished and non-pulsatile PBF; desaturation, endothelial dysfunction and lack of vessel recruitment during exercise (61). Poor function of the Glenn shunt can be suspected in the context of significant cyanosis, congestion in upper body and low cardiac output.

Every candidate for a Fontan procedure should undergo prior cardiac catheterization. A mPAP ≤15 mmHg, a mean TPG ≤6 mmHg, and PVRi ≤3 WU·m$^2$ are accepted cut-off values for patient's selection, even though they originate from expert opinion rather than large scale studies (62).

However, fulfilling these criteria does not predict a working Fontan in the long run, as PVR can increase years after procedure. Mechanisms for increased PVR are probably multifactorial. Loss of pulsatility in the pulmonary vascular bed impacts vascular recruitment, pulmonary vessels growth and endothelial function (63). Ageing is

also a potential contributor to worsened hemodynamics, as it has been shown that not only PAP but also LAp with consecutive left diastolic dysfunction increase with age (64). Lung biopsies from deceased failing Fontan patients show pulmonary vascular remodeling with media thinning, intimal fibrosis and collagen deposition and thrombosis *in situ*. Moreover, distal pulmonary arterioles overexpress endothelial NO synthase and endothelin receptors, markers of endothelial dysfunction (65,66).

An elevation of the mPAP in Fontan patients can lead to Fontan failure, protein-losing enteropathy, and plastic bronchitis. PVD in single ventricle physiology is not covered in the last international PH guidelines, in part because it rarely fulfills the definition of PH with a mPAP >20–25 mmHg. Nevertheless, PVD in the Fontan circulation impacts survival in a significant manner. This entity will have to be addressed in the next guidelines set.

### *Treatment*

Further studies are needed to show that targeted therapies are safe and efficient in the Fontan population (63,67). However, it makes intuitive sense to treat failing Fontan with increased PVR with pulmonary vasodilators. Published data have shown contrasted results so far (68-72). Some studies have shown some improvement in exercise capacity and symptoms after Fontan operation in patients treated with PDE-5 inhibitors and ERA (71-73). The Fontan Udenafil Exercise Longitudinal (FUEL) study was the first large-scale clinical trial to demonstrate a positive effect of 26 weeks of a PDE-5 inhibitor treatment on measures of exercise performance in adolescents after Fontan, although it failed to improve the main outcome of improved oxygen consumption at peak exercise (74).

Further research should aim to answer some of the following remaining questions: "Can Fontan patients benefit from targeted therapies?", and "Which Fontan patients should be treated with pulmonary vasodilators?", "When to start treatment, and on what criteria?", and "Which pulmonary vasodilator is most appropriate in this particular PVD?" (63,75).

There is no current evidence supporting the best management for patients with PVD at the Glenn stage, not eligible to continue down the univentricular pathway. Aorto-pulmonary shunt creation, with or without Glenn takedown, heart-lung transplantation or treatment with pulmonary vasodilators and Fontan completion are some of the existing strategies.

## Conclusions

Functional limitation and survival of PAH patients remain unsatisfactory despite tremendous progresses in the diagnostic and management of PAH made over the last three decades. In the absence of curative treatment of PH, PAH-CHD prevention by early closure of a congenital systemic-to-pulmonary shunt should be a priority. Defining precise preoperative parameters predicting a good outcome after surgical closure in patients with PAH-CHD and a mild to moderate elevation of PVR is necessary. Identifying non-invasive biomarkers correlated to the severity of PVD would help management. Pulmonary vasodilators are widely used in PAH-CHD. The benefit of upfront combination therapy is not as clearly demonstrated as in other PAH etiologies. Strategies to conduct clinical trials in pediatric PAH should be developed, including identification of age-specific surrogate endpoints.

Studies in PH-LHD should be carefully designed, and powered enough to detect a treatment effect in the proportion of patients with CpcPH.

Patients with an univentricular palliation with PVD should be included in multi-center pulmonary vasodilators drug trials to gather evidence about the use of specific therapies in this very peculiar group.

PH in the setting of CHD is a complex and evolving field. Patients should be managed in tertiary centers with PH expertise in order to benefit from a standardized and complete diagnostic workup, undergo baseline and follow-up heart catheterization in a safe environment, be treated according to the latest guidelines and have the opportunity to participate in clinical trials to improve scientific knowledge on this rare disease.

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