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REVIEW TOPIC OF THE WEEK

Pulmonary Hypertension in Infants, Children, and Young Adults

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ABSTRACT

Pulmonary hypertension (PH) in neonates, infants, children, adolescents, and young adults is a complex condition that can be associated with several cardiac, pulmonary, and systemic diseases contributing to morbidity and mortality. The underlying pulmonary hypertensive vascular disease (PHVD) is characterized by inflammation, pulmonary vascular remodeling, and angio-obliteration leading to elevated pulmonary arterial pressure and resistance, right ventricular dysfunction, left ventricular compression, and subsequent heart failure. Recent advancements in PH-targeted therapies and interventional-surgical procedures have contributed to the improvement in quality of life and survival in PH/PHVD. This paper gives an update on recent developments in the diagnosis and treatment of children and young adults with PH. The focus is on the heterogeneous etiology/pathophysiology of PH in the young, and particularly on PHVD associated with congenital heart disease. Moreover, new pharmacological, surgical, and interventional therapies and their practical application in progressive/severe pulmonary arterial hypertension with inadequate response to conventional pharmacotherapy are discussed. (J Am Coll Cardiol 2017;69:2551–69) © 2017 by the American College of Cardiology Foundation.

Pulmonary arterial hypertension (PAH) is characterized by progressive obliteration of small pulmonary arteries, leading to increased pulmonary vascular resistance (PVR), right heart failure, and death in ≈25% to 60% of patients 5 years after diagnosis (1,2). Recently, consensus statements have been developed specifically to guide the care of children with pulmonary hypertension (PH) (3,4). Typical challenges in the management of pediatric PH include the complexity of the underlying etiologies, the frequent comorbidities (i.e., prematurity, neonatal lung diseases [bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD), lung hypoplasia]), chromosomal anomalies, polymalformation syndromes, and the lack of pediatric trial data (5,6). This paper focuses on typical, rather specific features of PH in the young (**Central Illustration**), particularly PAH associated with congenital heart disease (CHD), determinants of risk for poor outcome (**Figure 1**), and recent developments in the diagnosis and treatment of PAH pulmonary hypertensive vascular disease (PHVD). The genetics of PAH, as well as the clinical PH that typically presents in the first year of life and is associated with developmental and/or parenchymal lung disease, are outlined very briefly, and are discussed in detail elsewhere (7,8).

DEFINITION AND CLASSIFICATIONS

PH is usually defined as a mean pulmonary artery pressure (mPAP) ≥25 mm Hg at rest, measured by cardiac catheterization (according to the 2015 European Society of Cardiology European Respiratory Society guidelines [2] and the Fifth World Symposium on PH, Nice, France, 2013 [9]). In children >3 months of age at sea level, PH is evident with an mPAP ≥25 mm Hg (10,11) (**Table 1**). The term PAH (i.e., group 1 PH) describes a subpopulation of patients with PH, characterized hemodynamically by pre-capillary PH, including an end-expiratory pulmonary artery wedge

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ABBREVIATIONS AND ACRONYMS

CHD = congenital heart disease

ES = Eisenmenger syndrome

HPAH = heritable pulmonary arterial hypertension

IPAH = idiopathic pulmonary arterial hypertension

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PAH = pulmonary arterial hypertension

PH = pulmonary hypertension

PHVD = pulmonary hypertensive vascular disease

PPHN = persistent pulmonary hypertension of the newborn (PH group 1″)

VO_2 = oxygen uptake

pressure (PAWP) (synonymous with pulmonary capillary wedge pressure [PCWP], but not with pulmonary capillary pressure) ≤15 mm Hg and a pulmonary vascular resistance (PVR) >3 Wood units (WU) (in children: PVR index >3 WU × m^2) (2,12). Although this definition of PAH using PVR indexed to body surface area has been widely accepted for pediatric use (**Tables 1 and 2**), in 2011, the Pulmonary Vascular Research Institute (PVRI) introduced the term *pediatric pulmonary hypertensive vascular disease* (mPAP ≥25 mm Hg and PVR index >3 WU × m^2 for biventricular circulation), 10 main PHVD categories, and more than 100 subcategories (PVRI Panama Classification, 2011) (**Table 3**) (13). Importantly, the Panama classification distinguishes between PH with and without pulmonary vascular disease (PVD), distinguishes between single and biventricular circulations (**Table 3**), and acknowledges the heterogeneous etiology of pediatric PH, which can even have pre-natal (fetal) origins. Fetal pathologies associated with post-natal PH include developmental lung diseases (congenital diaphragmatic hernia [CDH], lung hypoplasia with or without CDH, alveolar capillary dysplasia, surfactant protein abnormalities/deficiencies, pulmonary interstitial glycogenosis, pulmonary alveolar proteinosis, pulmonary lymphangiectasia) (**Table 4**) and perinatal insults such as chorioamnionitis (persistent pulmonary hypertension of the newborn [PPHN], BPD), meconium aspiration (PPHN), and/or birth asphyxia (PPHN).

EPIDEMIOLOGY AND CLINICAL AND GENETIC RISK FACTORS

Although PAH is a rare disease, with an estimated prevalence of 15 to 50 cases/million adults (14,15) and 2 to 16 cases/million children (16–18), its frequency in certain at-risk groups is substantially higher (e.g., human immunodeficiency virus, systemic sclerosis, schistosomiasis). Of note, high-risk conditions and untreated congenital or acquired heart disease are far more common in developing countries with limited health care; hence, the true, global burden of PHVD is widely underestimated. Untreated idiopathic pulmonary arterial hypertension (IPAH) results in death within 2 to 3 years in adults and within 1 year after diagnosis in children (19). In the pre-prostacyclin era (before 1995), children treated for IPAH had a poorer prognosis than adults, with a median survival of only 10 months versus 2.8 years, according to the National Institutes of Health registry. In a U.K. cohort study (reported clinical follow-up ended in 2007), the 5-year survival for children with PAH versus historical control subjects was still only 75%, with a freedom from death or transplantation of only 57% (17). Pediatric PAH is associated with impaired growth, especially in younger children (0 to 5 years of age) and in those with PAH-CHD (20). Such failure to thrive has been reported to be associated with a higher risk of death (17). Although adults with Eisenmenger syndrome (ES)-PAH have a somewhat better survival than those with IPAH or heritable pulmonary arterial hypertension (HPAH), children with either PAH-CHD/PHVD-CHD or IPAH/HPAH have a similar 5-year mortality (29% vs. 25%, REVEAL [Registry to Evaluate Early and Long-Term PAH Disease Management]) (1). The severity of adult PAH-CHD tends to be underestimated because the apparent survival is related to the immortal bias selection of patients in reported registries. The PAH outcome with lung or heart-lung transplantation is far from ideal, with a median 5-year post-transplant survival of ≈45% to 55% for adults with PAH, although high-volume transplant centers may achieve better outcomes (21,22). Determinants of risk for poor outcome in children with PAH (hospitalization because of PAH deterioration, lung transplantation, and/or death) are summarized in **Figure 1**, and a general diagnostic algorithm is outlined in **Figure 2**.

Currently, the evidence for causation in human IPAH and HPAH is considered sufficient for abnormalities in the genes *ACVRL1 (ALK-1), BMPR2, CAV1, ENG,* and *KCNK3;* a causal role for mutations in the *BMPR1B, NOTCH3,* and *SMAD9* genes is still unconfirmed (8). *BMPR2* is the major gene associated with HPAH and IPAH. More than 300 *BMPR2* mutations have been identified in PAH, and they are found in ≈75% HPAH and up to 25% of IPAH cases.

ETIOLOGIES AND PATHOBIOLOGY OF DISTINCT PH SUBGROUPS

PAH ASSOCIATED WITH CHD. Besides IPAH/HPAH (see the preceding text), a very common form of PAH diagnosed in childhood is PAH associated with CHD (all belong to group 1 PH) (**Table 2**). PAH-CHD often contains a pre- and/or post-tricuspid shunt lesion with or without pulmonary vascular disease (PVD) (23), and distinct patterns of right ventricular (RV) hypertrophy (24). Children without PVD benefit from closure of a left-to-right (systemic-to-pulmonary) shunt early in life. However, children and young adults with CHD-PAH *and* significant PVD (PHVD; i.e., high PVR and systemic-to-suprasystemic pulmonary artery pressure [PAP]; bidirectional or right-to-left shunt through the defect) may not tolerate such

CENTRAL ILLUSTRATION Common Differences in the Etiologies of Pediatric and Adult Pulmonary Hypertension

Pediatric Pulmonary Hypertension (PH)	Pediatric and Adult PH	Adult PH
• Genetic syndromes • Persistent PH of the newborn • Bronchopulmonary dysplasia • Developmental abnormalities (Alveolar capillary dysplasia, congenital diaphragmatic hernia) • Left ventricular (LV) outflow tract obstruction • Glycogen storage disease	• Idiopathic pulmonary arterial hypertension (PAH) • Heritable PAH • Congenital heart disease – PAH • Connective tissue disease – PAH • Portopulmonary hypertension • Interstitial lung disease • Cardiomyopathies • Myocarditis • Connective tissue disease • Drug-induced (chemotherapy) • Chronic hemolytic anemia • Other conditions: Sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis *Pathophysiological events:* *- Right ventricular (RV) hypertension* *- RV hypertrophy and maladaptation* *- RV dysfunction and failure* *- LV compression, LV underfilling* *- Low cardiac output syndrome* *- RV-LV interactions*	• Drug-induced PAH • Chronic obstructive pulmonary disease • Sleep-disordered breathing (obstructive sleep apnea) • Chronic thromboembolic PH • Chronic exposure to high altitude – PH • Ischemic left heart disease • Chronic arterial hypertension • Chronic renal failure • Myeloproliferative disorders *Pathophysiological events:* *- Alveolar hypoxia, respiratory acidosis* *- RV hypertension* *- LV systolic / diastolic dysfunction (heart failure with depressed ejection fraction / heart failure with preserved ejection fraction)* *- Postcapillary PH* *- Combined pre- and postcapillary PH*

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Pulmonary hypertension (PH) in children frequently occurs with congenital heart disease, with genetic syndromes, and as persistent PH in newborn and young infants, whereas idiopathic, heritable, drug-induced, and connective tissue disease–associated pulmonary arterial hypertension (PAH) are the primary etiologies of PH in adults. Moreover, interstitial lung disease, bronchopulmonary dysplasia, and developmental lung disease are commonly associated with PH in childhood, whereas chronic obstructive pulmonary disease and sleep-disordered breathing with diffusion impairment, alveolar hypoxia, and carbon dioxide retention are frequent causes of PH in adults. Post-capillary PH due to left heart disease is rare in children, but increasingly diagnosed in adults with left ventricular diastolic dysfunction. PAH (pre-capillary PH) is more and more considered a systemic disorder affecting multiple organ systems including heart, lung, liver, kidney, skeletal muscle, and connective tissue. LV = left ventricle/ventricular; PH = pulmonary hypertension; RV = right ventricle/ventricular.

shunt closure because high PVR persists, and the right ventricle (RV) may fail immediately or months after closure (**Figure 3**). The onset and progression of pulmonary vascular disease in PAH-CHD with left-to-right shunt differs widely, depending on whether the lesions are localized pre or post the tricuspid valve.

Post-tricuspid lesions are left-to-right (systemic-to-pulmonary) shunts at high pressure levels, which lead to volume load on the left ventricle (LV) and volume/pressure load to the pulmonary circulation (e.g., a large ventricular septal defect [VSD]). If the post-tricuspid defects are big enough, the PAP will increase to

FIGURE 1 Determinants of Risk in Pediatric PHVD

Pediatric Determinants of Risk in PHVD

Lower Risk	Determinants of Risk	Higher Risk
No	Clinical evidence of RV failure	Yes
No	Progression of symptoms	Yes
No	Syncope	Yes
Normal	Growth	Failure to thrive
I, II	WHO functional class	III, IV
Minimally elevated for age	Serum BNP / NT-proBNP	Greatly elevated for age > 1200 pg/mL (>1yr old) Rising NT-proBNP level
Minimal RA enlargement No RV enlargement No RV systolic dysfunction TAPSE >12mm (> 1yr old) S/D ratio < 1.0 (TR jet)	Echocardiography, CMR	Severe RA enlargement Severe RV enlargement RV systolic dysfunction TAPSE <10 mm (>1yr old) S/D ratio > 1.4 (TR jet) Pericardial effusion
CI >3.0 l/min/m^2 mPAP/mSAP <0.5 Acute vasoreactivity	Invasive Hemodynamics	CI <2.5l/min/m^2 mPAP/mSAP >0.75 mRAP >15 mm Hg PVRi >15 WU × m^2

The variables listed distinguish between lower risk and higher risk. The intermediate-risk group is broad and is not specifically defined. Overall, these determinants have only Level of Evidence: C, due to sparse or lacking pediatric data. Nevertheless, health care providers may use these variables as markers for poor outcome (hospitalization because of PAH deterioration, lung transplantation, and/or death). Health care providers may include the PVR/SVR ratio, the 6-min walk distance, and the maximum oxygen consumption (VO_2 max) obtained during cardiopulmonary exercise testing as risk variables; however, it is unclear where exactly the cutoff values should be set. One must also note that most of these variables have been validated primarily for IPAH, and the cutoff levels used earlier may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk. BNP = B-type natriuretic peptide; CI = cardiac index; CMR = cardiac magnetic resonance; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; mSAP = mean systemic arterial pressure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PHVD = pulmonary hypertensive vascular disease; PVR = pulmonary vascular resistance; PVRi = pulmonary vascular resistance index; RA = right atrium; RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation; VO_2 = oxygen uptake; WHO = World Health Organization.

systemic blood pressure level. In post-tricuspid lesions, PAH-PVD/PHVD will usually develop in the first years of life. If untreated, the majority of patients with post-tricuspid defects will develop suprasystemic PVR with reversal to a right-to-left shunt through the preformed shunt lesion (i.e., the so called ES) (25). In 153 ES patients of the German National Register for Congenital Heart Defects, the survival rate at 1, 5, and 10 years of follow-up was only 92%, 75%, and 57%, respectively, of the entire ES cohort, and was even worse in treatment-naive ES patients (86%, 60%, and 34%, respectively). Importantly, use of PAH-targeted therapy was independently associated with better survival (hazard ratio [HR]: 0.42) (26), as was higher oxygen saturation, presence of sinus rhythm, and absence of pericardial effusion in a recent retrospective, multicenter study (27).

Pre-tricuspid shunts are left-to-right (or bidirectional) shunts at low pressure levels (e.g., a large atrial septal defect [ASD]), which lead to a volume load on the RV and pulmonary circulation, but no immediate or midterm increase of PAP. In pre-tricuspid lesions, the development of PHVD may occur beyond the fourth decade of life in 6% to 17% (28). The risk of developing PVD is associated not only with the size of the ASD, but also with ventricular compliance. However, ES in ASDs is rare, and occurs in only 2% of adult patients (29). ASD closure is indicated for those with right heart dilation and normal PVR. Under these circumstances, prognosis is excellent, especially if closure is performed earlier in life (e.g., <25 years of age) (25,27). Clinical decision making is more difficult for patients with evidence for mild or moderate PVD (PVR elevation), because a subset will develop PAH after closure, and thus should not undergo proactive shunt closure (25). The clinical issues of older adults with CHD at risk for PAH and ES are discussed elsewhere (2,25,27,30,31).

CHD-PAH/PHVD not associated with left-to-right shunts, and CHD with PAH/PHVD persisting, progressing, or (re)occurring after corrective surgery of any cardiovascular defect, is quite a common condition in pediatric cardiology units. In particular, even after repair, conotruncal lesions (i.e., dextro transposition of the great arteries [d-TGA] [32]; truncus arteriosus, aortopulmonary septal defect [AP window, tetralogy of Fallot (TOF)/pulmonary stenosis]; pulmonary atresia with VSD [TOF/pulmonary atresia, double-outlet RV]; double-outlet LV, and others) appear to be associated with PAH/PHVD. Whether pre- or post-natal shear stress in systemic pulmonary shunt lesions, or abnormal fetal hemodynamics, genetic susceptibility, "fetal pulmonary arterial (PA) hyperoxia" or "fetal PA hypoxia due to poor mixing" (33) play a role in d-TGA/intact ventricular septum (IVS)-PPHN is unknown. Whatever the cause, when PPHN is suprasystemic in d-TGA/IVS, post-natal hypoxemia becomes severe, and response to balloon atrial septostomy is often poor; consequently, mortality is very high.

It is important to realize that CHD-PAH/PHVD, for example, in d-TGA/IVS, can occur as persistent PH in the newborn and young infant (34) with or without pulmonary interstitial glycogenosis (35) (**Table 4**), or may (re-)appear many years after the arterial switch operation (school-age or teenager) and progress all the way to end-stage PAH and bilateral lung transplantation (32). Importantly, conotruncal defects are frequently found in patients with *22q11.2 deletion*

syndrome (Di George), and such microdeletions have been equally associated with various types of isolated nonsyndromic conotruncal malformations (with the exception of TGA and double-outlet RV, where this association is very uncommon).

Patients with trisomy 21 (Down syndrome), with or without a significant left-to-right shunt (atrioventricular [AV] canal, VSD, primum ASD, TOF/AV canal), are at increased risk for PAH. Such risk exists pre- and post-operatively, and even without any surgery, in the presence or absence of a left-to-right shunt. If PAH develops, it may or may not respond to PAH monotherapy, for example, sildenafil (see also the section "Treatment of PAH associated with congenital heart disease").

PULMONARY VENO-OCCLUSIVE DISEASE AND PULMONARY CAPILLARY HEMOANGIOMATOSIS BELONG TO PH GROUP 1′. In the current PH classification (**Table 2**), pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemoangiomatosis (PCH) are considered a common entity representing varied expressions of the same disease. Biallelic mutations in the *EIF2AK4* gene were reported to be responsible for heritable cases of both PVOD (36) and PCH (36,37). Risk factors for nonidiopathic PVOD include chemotherapy, organic solvent or tobacco exposure, autoimmunity, and inflammatory conditions (sarcoidosis, Langerhans cell granulomatosis, Hashimoto's thyroiditis) (38,39). Clinically, PVOD and PCH often present after a delayed diagnosis in children and young adults, and similarly to IPAH in the young. PVOD and PCH are rarely responsive to pharmacotherapy, and the final diagnosis often is made by histological analysis, although radiological findings may be near-pathognomonic. Patients with PVOD/PCH usually have high oxygen demand, diffusion impairment with low diffusing capacity for carbon monoxide, and often suspicious findings on high-resolution chest computed tomography (CT) (centrilobular ground-glass opacities, smooth thickening of the interlobular septa, and frequently mediastinal lymph node enlargement). Pulmonary edema and pleural effusions either occur late or, typically, after initiation of vasodilator therapy (38,39). Moreover, it may be difficult to determine the PAWP (i.e., so-called PCWP) in PVOD, or the PAWP is normal or near-normal (PAWP ≤15 mm Hg).

PH IN NEONATES AND INFANTS (PPHN, ALVEOLAR CAPILLARY DYSPLASIA, CDH, BPD/CLD). After birth, PVR drops when post-natal levels of partial arterial pressure of oxygen and oxygen saturation increase (oxygenation), partial arterial pressure of carbon dioxide decreases (ventilation), and the arterial pH rises. *PPHN* (PH group 1″) (**Table 2**) is a syndrome resulting from maladaptation to extra-uterine life with sustained PVR elevation (**Table 3**). PPHN occurs in ≈2 of 1,000 live births (7), results in hypoxemia due to right-to-left shunting at the ductal and/or atrial level, and may coexist with CHD (see the previous text). PPHN is frequently idiopathic, but may be associated with respiratory failure/alveolar hypoxia, developmental lung diseases (**Table 4**), or pre-natal closure of the ductus arteriosus. PPHN might be life-threatening, but often is reversible within the first few days of life. However, an under-reported condition called *chronic progressive PH in infancy* has a mortality of 40% to 60%, and

TABLE 1 Definitions

PH
mPAP ≥25 mm Hg in children >3 months of age at sea level
PAH
mPAP ≥25 mm Hg
PAWP ≤15 mm Hg*
PVRi >3 WU × m^2
IPAH
PAH with no underlying disease known to be associated with PAH
HPAH
PAH with no underlying disease but with positive family history or positive genetic testing
PHVD
For biventricular circulations:
mPAP ≥25 mm Hg and PVRi >3 WU × m^2
For circulations with cavopulmonary anastomosis (e.g., Fontan physiology):
Mean TPG >6 mm Hg (calculate mPAP − mLAP or PAWP) or PVRi >3 WU × m^2
AVT to assess prognosis and indication for specific PH therapy • The hemodynamic change that defines a positive response to AVT in pediatric PH without shunt (Qp:Qs = 1:1) should be considered a more than 20% fall in mean PAP and PVRi/SVRi ratio without a decrease in cardiac output (i.e., positive acute vasoreactivity response in IPAH/HPAH)† • This is a modification of the Barst criteria (1986) for positive AVT.
AVT in patients with CHD and shunt to assess operability (**Figure 3**) • With significant L-R shunt, the aforementioned criteria need some modification due to different underlying pathophysiology. • The hemodynamic change that defines a positive response to AVT in PAH associated with a shunt defect (Qp:Qs >1.5; APAH-CHD shunt) for children should be considered as a more than 20% fall in PVRi and PVRi/SVRi with respective final values of PVRi <6 WU and PVRi/SVRi <0.3.
PAH associated with portal hypertension (PH group 1) is a rare condition in childhood that may occur in patients with liver disease and/or catheter-associated occlusion of the portal vein. PAH associated with connective tissue disease (CTD) (group 1 PH) is rare in childhood, with systemic sclerosis (up to 16%) and systemic lupus erythematosus probably carrying the highest risk for PAH development.

*Please note that PAWP ≤15 mm Hg is used in the European Society of Cardiology/European Respiratory Society 2016 Guidelines on Pulmonary Hypertension (2) and the 2013 PH World Symposium documents (11), but that PAWP <15 mm Hg is used in the American Heart Association/American Thoracic Society Guidelines on pediatric PH (4). †Detailed hemodynamic definitions of PH (e.g., pre-capillary vs. post-capillary PH, value of the diastolic transpulmonary pressure gradient, definition of acute vasoreactivity in PAH-CHD shunt lesions and PAH without a shunt) are presented in Apitz et al. (53).

APAH = associated pulmonary arterial hypertension; AVT = acute vasoreactivity testing; CHD = congenital heart disease; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; L-R = left-to-right; mLAP = mean left atrial pressure; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure (synonymous with pulmonary capillary wedge pressure; not synonymous with pulmonary capillary pressure); PH = pulmonary hypertension; PHVD = pulmonary hypertensive vascular disease; PVRi = pulmonary vascular resistance index; Qp = pulmonary blood flow; Qs = systemic blood flow; SVRi = systemic vascular resistance index; TPG = transpulmonary pressure gradient; WU = Wood unit(s).

TABLE 2 Clinical Classification of Pulmonary Hypertension*

1. Pulmonary arterial hypertension	
1.1 IPAH	
1.2 HPAH	1.2.1 BMPR2 1.2.2 Other mutations, e.g., ACVRL1 (Alk-1), ENG, SMAD9, CAV1, KCNK3
1.3 Drug and toxin induced	
1.4 Associated with:	1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart diseases 1.4.5 Schistosomiasis
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis	1′.1 Idiopathic 1′.2 Heritable 1′.2.1 EIF2AK4 mutation 1′.2.2 Other mutations 1′.3 Drugs, toxins and radiation induced 1′.4 Associated with: 1′.4.1 Connective tissue disease 1′.4.2 HIV infection
1″. Persistent pulmonary hypertension of the newborn	
2. PH due to left heart disease	2.1 LV systolic dysfunction 2.2 LV diastolic dysfunction 2.3 Valvular disease 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies 2.5 Congenital/acquired pulmonary vein stenosis
3. PH due to lung diseases and/or hypoxia	3.1 Chronic obstructive pulmonary disease 3.2 Interstitial lung disease 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern 3.4 Sleep-disordered breathing 3.5 Alveolar hypoventilation disorders 3.6 Chronic exposure to high altitude 3.7 Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstruction	4.1 Chronic thromboembolic pulmonary hypertension 4.2 Other pulmonary artery obstruction 4.2.1 Angiosarcoma 4.2.2 Other intravascular tumors 4.2.3 Arteritis 4.2.4 Congenital pulmonary artery stenoses 4.2.5 Parasites (hydatidosis)
5. PH with unclear and/or multifactorial mechanisms	5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders 5.4 Other: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis) segmental pulmonary hypertension

*Fifth World Symposium on Pulmonary Hypertension, Nice 2013 (9), and slightly modified in the European Society of Cardiology/European Respiratory Society Guidelines 2015 (2)

LV = left ventricular; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; other abbreviations as in Table 1.

TABLE 3 Panama Classification of PPHVD (2011): 10 Basic Categories

Category	PPHVD Category
1	Pre-natal or developmental pulmonary hypertensive vascular disease
2	Perinatal pulmonary vascular maladaptation
3	Pediatric cardiovascular disease
4	Bronchopulmonary dysplasia
5	Isolated pediatric pulmonary hypertensive vascular disease (isolated pediatric PAH)
6	Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes
7	Pediatric lung disease
8	Pediatric thromboembolic disease
9	Pediatric hypobaric hypoxic exposure
10	Pediatric pulmonary vascular disease associated with other system disorders

Reprinted with permission from del Cerro et al. (13).

PAH = pulmonary arterial hypertension; PPHVD = pediatric pulmonary hypertensive vascular disease.

may represent early onset IPAH or other PH subtypes; the most common etiologies include BPD, CDH, interstitial pneumonia, and CHD (40).

PH associated with BPD/CLD mainly develops in very pre-term infants as a result of impaired vascular and alveolar lung development (7). About 25% of infants with moderate to severe BPD develop PH (41), which greatly increases mortality (47% die 2 years after diagnosis of PH) (42). For other developmental and parenchymal lung diseases associated with PH, see Table 4 and the corresponding consensus statement of the European Pediatric PVD Network (43).

DIAGNOSIS, MONITORING, AND PROGNOSIS

ECHOCARDIOGRAPHY, CARDIAC MAGNETIC RESONANCE, CT, AND CARDIAC CATHETERIZATION. Although the definite diagnosis of PH and PHVD is made by cardiac catheterization, using the current definition (Table 1), the first diagnostic tool in suspected PH is generally the transthoracic echocardiogram (Figures 1 to 3) (3,10). *Echocardiography* not only allows a comprehensive initial assessment of cardiovascular anatomy, but may also confirm RV pressure elevation by estimative Doppler interrogation (44). Due to variable body size and different causal pathophysiology, pediatric echocardiographic variables have specific reference ranges (45) and a variable effect on the accuracy of the diagnosis of PH in children versus adults. Combining commonly-used and more novel echocardiographic variables (e.g., right atrial [RA] size [45,46]; tricuspid annular peak systolic excursion; right ventricular outflow tract velocity time integral [RVOT VTI]; tricuspid regurgitation velocity/RVTO VTI ratio [47]; RV size [46], LV size, and RV/LV ratio [48]; RV stroke work [49]; LV strain/strain rate [50]; and pulmonary artery acceleration time [51]) to assess RV/LV function and size, as well as pulmonary blood flow in pediatric PH, may help the clinician to avoid some of the pitfalls of echocardiography, especially the over-reliance on the Doppler pressure estimation in the assessment of children with PH (44).

Cardiac magnetic resonance (CMR) and CT are recommended noninvasive imaging modalities in the management of PH (52). CMR offers the ability to assess ventricular function, blood flow, pulmonary perfusion, and myocardial tissue characteristics. The main role of CT is to detect lung parenchymal disorders, thromboembolic disease, and vascular abnormalities such as pulmonary vein stenosis. If sedation/anesthesia is needed for either CMR or CT, the risk needs to be balanced against the potential gain of information and its effect on the future therapy.

Diagnostic cardiac catheterization with acute pulmonary vasoreactivity testing (AVT) (**Table 1**) should be performed in almost all patients before the initiation of PAH-targeted therapy (**Figures 2 and 3**). Exceptions to this recommendation may be premature infants at high risk and/or very low body weight, and children with systemic vasculopathies or hemodynamic instability (53,54). A systematic catheterization protocol is required, and has been established in a very standardized manner for adults, and recently also for pediatric PH (53). However, the complexity of childhood PVD often requires an individualized approach.

BIOMARKERS IN PH. Serum/plasma B-type natriuretic peptide (BNP) and its N-terminal cleavage product (NT-proBNP) are secreted by cardiomyocytes in response to atrial/ventricular wall stress due to pressure/volume overload. Although their proportional secretion and age dependence are similar, NT-proBNP has a longer half-life than BNP (118 min vs. 18 min) (**Table 5**). Troponin T (TnT) is a marker for myocardial cell damage. The relative changes of NT-proBNP/BNP and high-sensitivity TnT and their association with outcome make them prognostic biomarkers in adult PAH. In a meta-analysis of 25 small pediatric studies, NT-proBNP (HR: 3.2), World Health Organization functional class (WHO-FC) (HR: 2.7), indexed PVR (HR: 1.3), mean right atrial pressure (HR: 1.1), cardiac index (HR: 0.7), and acute vasodilator response (HR: 0.3) were identified as significant prognostic factors in pediatric PH (55) (**Figure 1**). Serial assessment of such biomarkers is advisable, as the dynamics of their concentrations are often more indicative of severity and progression of PAH than their absolute values. Moreover, plasma galectin-3, a β-galactoside-binding lectin that acts downstream of the mineralocorticoid receptor in smooth muscle cells, is increased in both IPAH and connective tissue disease-associated PAH, and correlates with PAH severity (WHO-FC) in adults (56). Plasma galectin-3 concentrations are also elevated among adults with CHD and a Fontan circulation, and are associated with an increased risk of nonelective cardiovascular hospitalization or death (HR: 9.2) (57).

TABLE 4 Developmental Lung Diseases Associated With PH

Developmental Defect	Vascular Pathology
Alveolar capillary dysplasia with or without misalignments of veins	Reduction of alveolar capillaries, thickening of alveolar septal tissue, and an apparent failure of the capillaries to make contact with the alveolar epithelium. Familial cases occur. Genetic deletions and point mutations within the FOX transcription factor gene cluster at 16p24.1 and FOXF1 were identified.
Bronchopulmonary dysplasia	Pre- and post-natal effect of exogenous risk factors on a structural and functional immature lung lead to *post-natal impairment of angiogenesis* and alveolarization associated with *abnormal vascular function* (increased tone, altered reactivity, impaired metabolism) and *structure* (smooth muscle cell proliferation, altered extra cellular matrix structure).
Congenital diaphragmatic hernia	Developmental defect leading to severe vascular remodeling and rarefication of the vascular bed.
Lung hypoplasia (primary and secondary)	Genetic abnormalities or severe reduction in amniotic fluid leading to reduced pre-natal alveolar and vascular development.
Pulmonary interstitial glycogenosis	Rare, nonlethal pediatric form of interstitial lung disease, possible male predominance. Infants present with respiratory distress. Histological characteristics are the accumulation of monoparticulate glycogen in interstitial cells and associated lung growth abnormalities affecting all lung structures.
Pulmonary alveolar proteinosis	Rare lung disease in which abnormal accumulation of surfactant occurs within the alveoli, interfering with gas exchange and affecting lung growth. Possible cause anti-GM-CSF autoantibodies.
Pulmonary lymphangiectasia	Rare developmental pulmonary disorder characterized by pulmonary subpleural, interlobar, perivascular, and peribronchial lymphatic dilation.
SP abnormalities (SP-B and SP-C deficiency, ATP binding cassette A3 mutation, thyroid transcription factor 1/Nkx2.1 homeobox mutation)	Genetic inheritance of surfactant deficiency leading to impaired lung development.

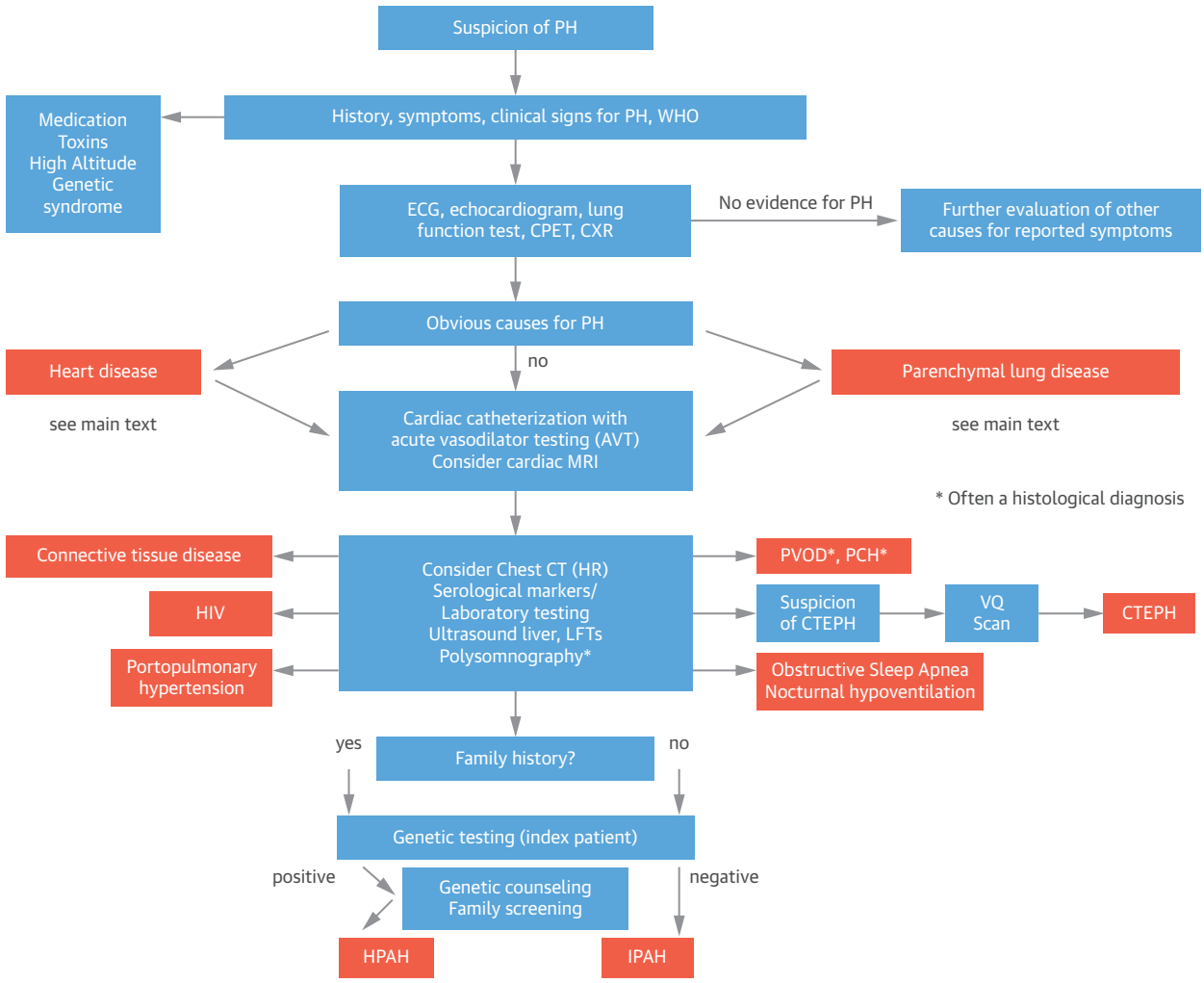
Modified with permission from Hilgendorff et al. (7).

ATP = adenosine triphosphate; FOX = forkhead box; GM-CSF = granulocyte-macrophage colony stimulating factor; PH = pulmonary hypertension; SP = surfactant protein.

TREATMENT

During the past few years, treatment of PAH has undergone a remarkable evolution, which has led to the current approval of 5 different classes of drugs for adults (i.e., phosphodiesterase-5 [PDE5] inhibitors, soluble guanylate cyclase stimulators, endothelin receptor antagonists [ERAs], prostacyclin analogs, and prostacyclin receptor agonists) using 4 different routes of administration (oral, inhaled, subcutaneous, and intravenous). Modern drug therapy led to a significant improvement in patients' symptomatic status and a slower rate of clinical deterioration (2). However, therapeutic strategies for adult PAH have not been sufficiently studied in children, so that only

FIGURE 2 Diagnostic Algorithm for Suspected or Confirmed PH in Children and Young Adults



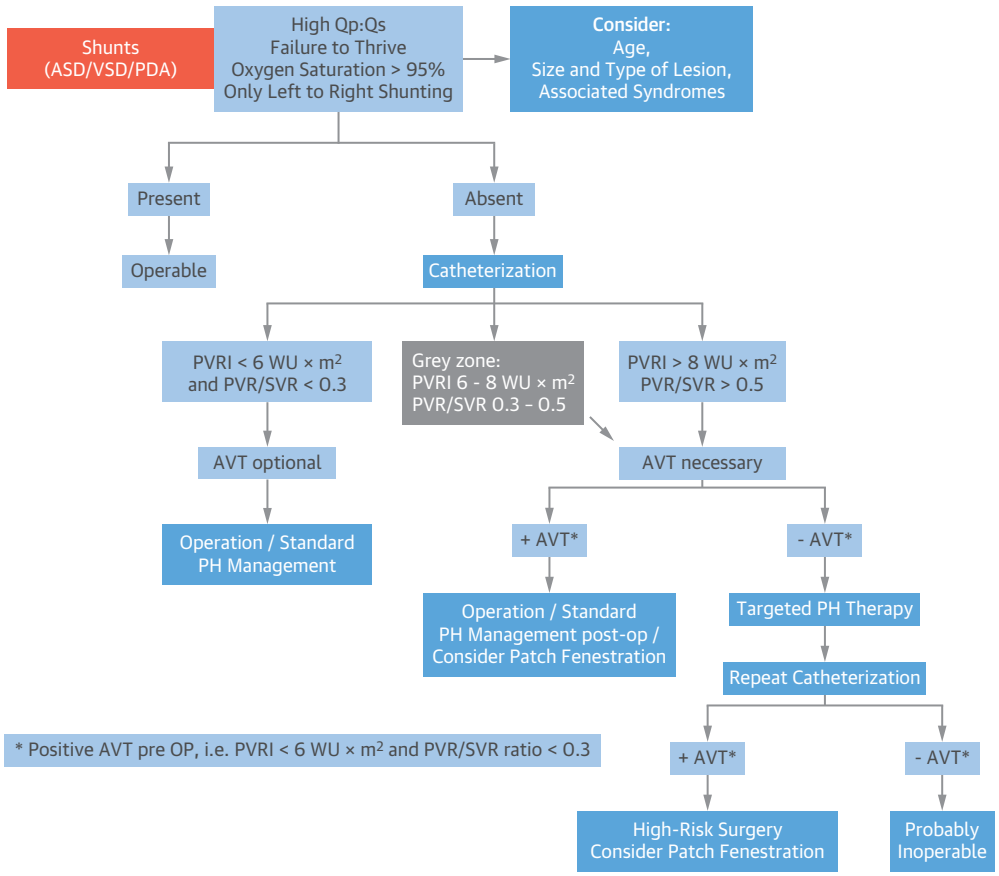
Screening for pediatric PH is performed by ECG and echocardiography. If these investigations suggest the presence of pulmonary hypertension (PH)/pulmonary hypertensive vascular disease (PHVD), chest x-ray, and/or chest CT should be considered, followed by additional investigations. If PH/PHVD is severe, and the patient presents severely ill in overt heart failure and/or pulmonary vascular crisis, cardiac catheterization may be postponed and pharmacotherapy including intravenous prostanoids started immediately. Reprinted with permission from Lammers et al. (9). AVT = acute vasoreactivity testing; CPET = cardiopulmonary exercise testing; CT = computed tomography; CTEPH = chronic thromboembolic pulmonary hypertension; CXR = chest X-ray; ECG = electrocardiogram; HIV = human immunodeficiency virus; HPAH = hereditary pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; LFT = liver function test; MRI = magnetic resonance imaging; PCH = pulmonary capillary hemangiomatosis; PH = pulmonary hypertension; PVOD = pulmonary veno-occlusive disease; VQ = ventricular perfusion; WHO = World Health Organization.

a minority of these drugs has been officially approved for use in children.

Thus, appropriate therapies must be selected after a careful and comprehensive review in a PH expert referral center according to current international recommendations (3,4,58). For example, PAH-CHD indeed requires a different treatment approach than PH associated with BPD or diaphragmatic hernia. **Figures 4 and 5** outline algorithms for the treatment of pediatric PAH; detailed recommendations and comprehensive drug information are given elsewhere (58).

The overall goal of PAH therapy is to induce: 1) pulmonary arterial vasodilation (plus, at best, anti-inflammation and reverse remodeling); 2) to unload pressure and support the RV; 3) to avoid coronary ischemia and heart failure; and 4) to achieve improvement of clinical symptoms (i.e., exercise tolerance) (58). Of note, this approach does not necessarily apply to patients with PVOD or pulmonary

FIGURE 3 Algorithm for Management of Patients With CHD Associated With PAH/PHVD and Congenital Shunt Lesions



The indication for invasive diagnostics and eligibility for surgery/operability by comprehensive right and left heart catheterization includes basic evaluation and AVT, the latter especially in the gray zone of forecast uncertainty. Modified with permission from Lopes and Barst (89). ASD = atrial septal defect; AVT = acute vasoreactivity testing; PAH = pulmonary arterial hypertension; PDA = patent ductus arteriosus; pre-OP = pre-operatively; Qp = pulmonary blood flow; Qs = systemic blood flow; VSD = ventricular septal defect; WU = Wood units; other abbreviations as in Figures 1 and 2.

capillary hemangiomatosis who can deteriorate with vasodilator therapy (however, some patients benefit from low-dose prostacyclin analog therapy).

If the responder criteria of acute vasoreactivity testing with inhaled NO + oxygen in the cardiac catheterization laboratory are fulfilled (Table 1), *calcium-channel blocker (CCB)* therapy is still the treatment of choice for pediatric IPAH/HPAH (Figures 4 and 5). For nonresponders, or those who show fading vasoreactivity and deterioration on CCBs, oral or parenteral therapy currently targets 3 main pathways:

- Nitric oxide (NO) pathway
- Endothelin pathway
- Prostacyclin pathway

Remarkably, to date, only 2 PAH-targeted drugs have been approved by regulatory agencies (Food and Drug Administration [FDA] and European Medicines Agency [EMA]) for use in children: sildenafil (body weight ≥8 kg and age >1 year) and Bosentan (age >1 year). Additional PAH medications are frequently used in children and adults for PAH associated with IPAH/HPAH and repaired CHD.

SILDENAFIL. Sildenafil is an orally active inhibitor of PDE5, inducing vasodilation and exhibiting antiproliferative effects through the NO/cyclic guanosine monophosphate pathway within the pulmonary vasculature. Randomized controlled trials (RCTs) in adult PAH patients treated with sildenafil have confirmed favorable results on exercise capacity,

TABLE 5 NT-proBNP Serum Concentrations in Healthy Neonates, Infants, and Children (Reference Values)

	Sex	n	Range (pg/ml)	Mean (pg/ml)	SD (pg/ml)	Median (pg/ml)
UCB	All	62	281–2,595	818	546	668
Day 0–1	All	8	273–13,224	6,072	4,930	4,558
Day 2–3	All	40	621–8,122	2,972	1,808	2,492
Day 4–8	All	11	243–4,130	1,731	1,236	1,321
Day 9–365	All	26	48–739	215	169	157
Yr >1–10	All	55	5–675	107	110	77
Yr >10–13	F	16	5–157	50	35	43
	M	14	8–150	54	50	30
Yr >13–18	F	11	9–162	69	49	68
	M	15	5–161	42	50	23
Yr >18–57	F	17	11–145	77	43	72
	M	9	5–32	14	10	9

Reprinted with permission from Schwachtgen et al. (98).

NT-proBNP = N-terminal pro-B-type natriuretic peptide; UCB = umbilical cord blood.

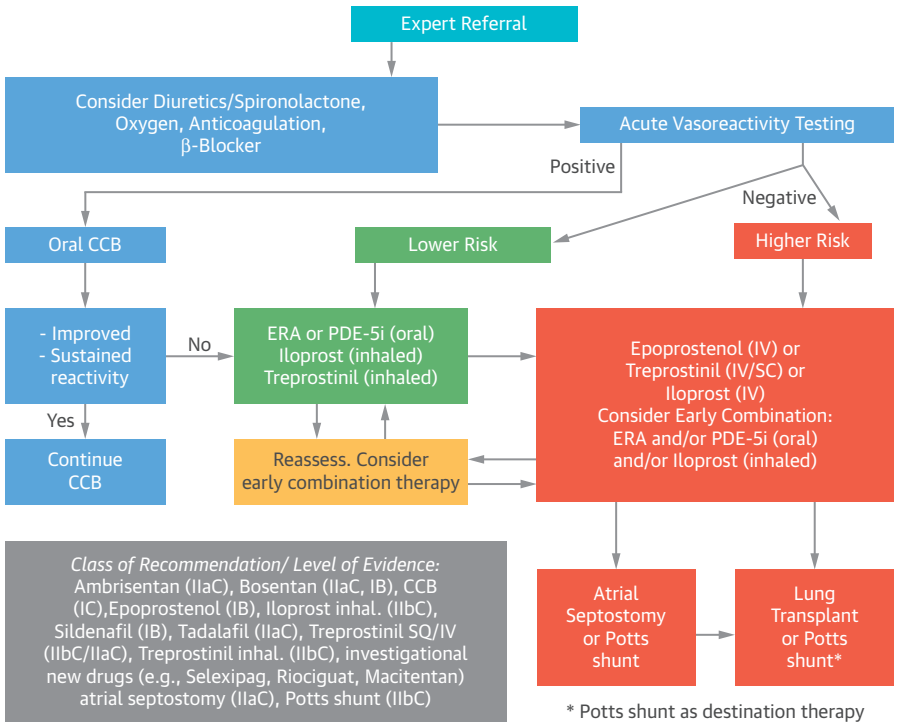
symptoms, and hemodynamics. STARTS (Sildenafil in Treatment-naive children, Aged 1-17, with pulmonaRy arTerial hypertenSion)-1 (59) and STARTS-2 (60) are the first pediatric randomized, placebo-controlled RCTs, conducted in treatment-naive children with PAH. In STARTS-1, children with PAH, 1 to 17 years of age (≥8 kg body weight), received low- (10 mg), medium- (10 to 40 mg), or high-dose (20 to 80 mg) sildenafil or placebo orally 3 times daily for the duration of 16 weeks. There was no statistically significant benefit for each sildenafil dosing group versus placebo in terms of the primary outcome measure, peak oxygen consumption (VO_2 max), as assessed by cardiopulmonary exercise testing. However, in the subgroup analysis, functional capacity significantly improved in the high-dose sildenafil group, and the PVR index was lowered with medium- and high-dose sildenafil. Unfortunately, there was a rise in mortality that was significantly higher in the high-dose sildenafil versus placebo group. These results led to different recommendations by the EMA and FDA. In 2011, sildenafil received EMA approval for use in children >1 year of age (10 mg 3× daily for weight <20 kg, and 20 mg 3× daily for weight ≥20 kg). The higher mortality in the high-dose sildenafil group resulted in an EMA warning not to use higher doses in 2013. The FDA even released a warning against the (chronic) use of sildenafil in children with PAH between 1 and 17 years of age in 2013, which was clarified in 2014 ("no contraindication" for pediatric use of sildenafil). In STARTS-2 (60), the 16-week blinded extension study of STARTS-1, HRs for mortality were 3.95 (95% confidence interval [CI]: 1.46 to 10.65) for high-dose versus low-dose and 1.92 (95% CI: 0.65 to 5.65) for medium-dose versus low-dose sildenafil; however, multiple analyses raised uncertainty about the survival-dose relationship (60). Importantly, children with PAH-CHD and those weighing <20 kg (or >45 kg) did not appear to be at an increased risk with high-dose sildenafil in the STARTS-1 and -2 trials.

BOSENTAN. Bosentan is an oral active dual endothelin-A and -B receptor antagonist (ERA for ET_A and ET_B) that should combat the vasoconstrictor and mitogenic effects of the endothelin-1 pathway that is activated in PAH patients. Multiple RCTs on bosentan in adults with PAH (idiopathic, associated with CHD and connective tissue disease) showed improvement in exercise capacity, functional class, hemodynamics, echocardiographic variables, and time to clinical worsening. Retrospective observational studies and case series demonstrated that bosentan therapy is safe and appears to be effective in slowing disease progression in children with PAH. In a retrospective study of 86 children treated with bosentan with or without concomitant therapy, bosentan was associated with sustained hemodynamic and clinical improvement, and an estimated 2 year-survival of 91% (61). However, at 4 years, disease progression in the children on bosentan was high (54%), with an estimated survival of 82% (62). A total of 69 children (≥2 and <12 years of age) were enrolled in the FUTURE-1 trial (Formulation of Bosentan in Pulmonary Arterial Hypertension) (63) and FUTURE-2 trial (64), both of which were primarily safety studies. In the placebo-controlled BREATHE-5 trial (Bosentan Randomized Trial of Endothelin Antagonist Therapy-5), bosentan improved exercise capacity and hemodynamics, with few adverse events, in adult PAH patients with ES (65). On the basis of the BREATHE-3 (66) and FUTURE-1 (63) trial data, the EMA approved the pediatric formulation of bosentan for use in children with PAH >1 year of age, with a maximum dose of 2 mg/kg/dose twice daily.

Elevation of serum liver aminotransferases may occur as a serious adverse event in bosentan therapy, but seem to be more frequent in adults and children ≥12 years of age (7.8%) than children <12 years of age (2.7%) (67). Nevertheless, it is recommended to perform liver function testing monthly in children who are receiving bosentan.

PROSTACYCLIN ANALOGS. Prostacyclin analogues activate the prostacyclin (PGI_2) receptor (IP receptor) and induce vasodilation in the pulmonary vasculature, inhibit proliferation of vascular smooth muscle cells, and probably exert anti-inflammatory effects. Inhaled prostacyclin (iloprost, treprostinil) is used in children with progressive or persistent PAH, usually as

FIGURE 4 Treatment Algorithm for IPAH and HPAH

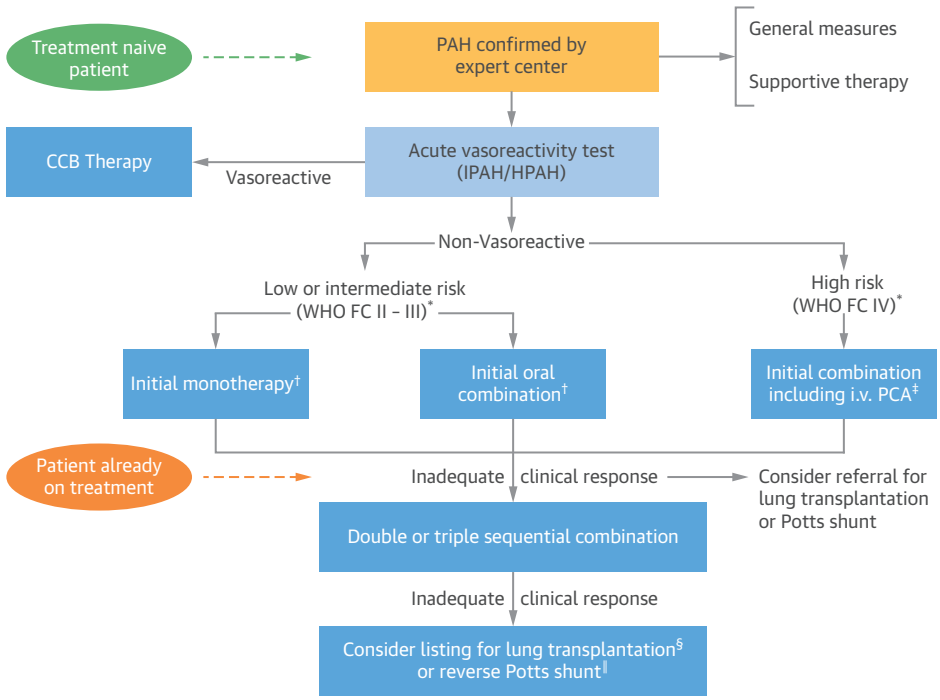


Solid clinical data on the therapy for other forms of PH is limited. The "intermediate-risk" group is broad, and not specifically defined. Health care providers may consider upfront, early, or rapid sequence-targeted PAH therapy in the "intermediate-risk" group (between "lower-risk" and "higher-risk" in **Figure 1**). Use of all agents, aside from sildenafil and bosentan, is considered off-label in children (>1 year of age) in Europe. Sildenafil dosing recommendations should follow EMA-approved dosing for children. Bosentan received the following dual grading: COR I, LOE B for children with PAH and Eisenmenger syndrome (ES), and COR IIa, LOE C for children with PAH without ES. Vasoreactivity testing is mainly useful for IPAH/HPAH, and these diagnoses form the basis for the body of published data. However, especially in pediatric PH, but also in adult PH, there may be PAH with a small, nonsignificant, or borderline pre-tricuspid (ASD, with Qp/Qs <1.5) or irrelevant post-tricuspid (VSD) LR shunt that does not explain the severe increase in PAP and PVR. In these occasions, patients with a progressive course may be better classified as having IPAH than PAH-CHD. In addition, positive vasoreactivity testing in the cardiac catheterization laboratory is associated with a better prognosis, and may help with deciding whether to close a left-to-right (= systemic-to-pulmonary arterial) shunt with borderline pulmonary vascular resistance. The addition of the reverse Potts shunt is a modification of the original figure, as there is according pediatric data available (92). Modified and expanded from Ivy et al. (10), and reprinted with modifications with permission from Hansmann and Apitz (54). CCB = calcium-channel blocker; COR = Class of Recommendation; ERA = endothelin receptor antagonist; inh. = inhalation; IV = intravenous; LOE = Level of Evidence; PDE-5i = phosphodiesterase 5 inhibitor; SC = subcutaneous; other abbreviations as in **Figure 2**.

an off-label, sequential combination therapy with an ERA and/or PDE5 inhibitor. The high frequency of required inhalations (6 to 8× per 24 h for iloprost, 4 to 6× per 24 h for treprostinil) has a negative effect on patient compliance, especially in school children and young adults. In patients with severe and/or progressive, therapy-resistant, high-risk PAH (WHO functional class III or IV), add-on or upfront subcutaneous treprostinil, intravenous epoprostenol, or intravenous treprostinil should be strongly considered.

EPOPROSTENOL (INTRAVENOUS INFUSION). Intravenous epoprostenol improves quality of life and survival in children and adults with IPAH (noncomposite primary outcome) (68-70). In retrospective analyses, children with IPAH who were treated with intravenous epoprostenol (n = 24; AVT nonresponders or those with CCB treatment failure) had a 4-year survival rate of 94% (69) and a 10-year freedom from death, transplantation, or atrial septostomy of 37% (13 of 35) (71). The combination of oral sildenafil, bosentan, or both with intravenous epoprostenol resulted in better survival in a U.K. observational cohort of children with PAH (17,72). The effective dose of epoprostenol is higher in children than in adults. Up-titration of epoprostenol is common, but excessive doses (>120 ng/kg/min) may lead to high-output states that require down-titration (73).

FIGURE 5 Treatment Algorithm for Treatment-Naive Patients With PAH



*Some WHO-FC III patients may be considered high risk. †Initial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure. ‡Intravenous epoprostenol monotherapy should be prioritized, as it has reduced the 3-month mortality rate in high-risk PAH patients. §Consider also balloon atrial septostomy. ‖Only small study results are available. Potts may be an alternative or bridge to lung transplantation in patients with systemic-suprasystemic RV pressure in the absence of severely impaired RV systolic function. The addition of the reverse Potts shunt is a modification of the original figure, because pediatric data on reverse Potts shunt therapy for PAH are available (84). Reprinted with permission from Galiè et al. (2). DPAH = drug-induced pulmonary arterial hypertension; PCA = prostacyclin analog; WHO-FC = World Health Organization functional class; other abbreviations as in Figures 2 to 4.

A new, more stable epoprostenol compound allows up to once-weekly preparation not requiring ice packs or special mixing diluents. Nevertheless, the short half-life of epoprostenol (2 to 5 min) keeps PAH patients at very high risk for pulmonary vascular crisis when there is a sudden problem with parenteral drug delivery.

TREPROSTINIL (SUBCUTANEOUS INFUSION, INTRAVENOUS INFUSION, AND INTERMITTENT INHALATION). Treprostinil is the tricyclic benzidine analog of epoprostenol that is sufficiently stable to be given continuously, intravenously, or subcutaneously at room temperature. Subcutaneous use of continuous treprostinil via mini pumps is often associated with side pain, but allows patients to live free of central venous catheters with their inherent complications: line infection, sudden occlusion, or extravasal dislocation. Add-on subcutaneous treprostinil has been studied in 8 PAH children at an average dose of 40 ng/kg/min, with acceptable side effects (74). Highly efficient intravenous treprostinil can be given by continuous infusion through small, external, or subcutaneously implantable intravenous pumps. In adults with PAH, the required dose of intravenous treprostinil appears to be 2 to 3× higher than the dose of epoprostenol (75). A retrospective study of intermittent treprostinil inhalation in 29 children with PAH (3 to 9 breaths, 6 μg/breath, 4× daily) showed promising results, with an improvement in WHO functional class and 6-min walk distance (6MWD) (76).

ILOPROST (INTERMITTENT INHALATION). Iloprost is delivered by simple nebulization in small children and by adaptive aerosol delivery in older children, adolescents, and adults. Iloprost should be administered 6 to 9× in 12 to 18 h (every 2 to 3 h, daily) (77). Since 2015, a new chip and higher-concentration ampules are available in Europe, which reduced the duration of inhalation from 10 to 15 min to 4 to 5 min. Iloprost

induces pulmonary vasodilation, and probably anti-inflammatory and antiremodeling effects, with only a moderate effect on systemic blood pressure. Headaches, jaw pain, and airway reactivity (78) may occur at the beginning of iloprost therapy; thus, pulmonary function tests are recommended before the start of any inhalative therapy. In adults, inhaled iloprost has been studied in combination with sildenafil (79) and bosentan (80), but phase 2/3 studies in children with PAH have not been conducted.

RECENT DRUG DEVELOPMENT FOR PAH THERAPY. *Macitentan*, a novel dual ERA, was developed by modifying the structure of bosentan to increase efficacy and safety. The SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcome) study demonstrated that macitentan decreased the composite endpoint of morbidity and mortality in adult patients with PAH, and also increased exercise capacity (81). There was no liver toxicity, but anemia (hemoglobin ≤8 g/dl) was observed in 4.3% of patients receiving 10 mg macitentan. In contrast to bosentan, macitentan is not known to lower the plasma levels of sildenafil. Two phase 3 RCTs on the use of macitentan in children with PAH from 2 to 17 years of age (TOMORROW [A Study to Find Out Whether the Medicine Macitentan Works in Children With Pulmonary Arterial Hypertension (PAH)]; NCT02932410) and patients with ES ≥12 years of age (MAESTRO-OL [Clinical Study to Assess the Long-term Safety, Tolerability, and Efficacy of Macitentan in Subjects With Eisenmenger Syndrome]; NCT01739400) are in preparation or ongoing.

Riociguat, another promising therapy, is an oral agent with a dual mode of action: it acts in synergy with endogenous NO and also directly stimulates soluble guanylyl cyclase (GC) independent of NO availability. PATENT (Pulmonary Arterial Hypertension Soluble Guanylate Cyclase-Stimulator Trial)-1 (82) was a phase 3, double-blind study that assigned 443 adult patients with symptomatic PAH to receive placebo, riociguat in individually-adjusted doses of up to 2.5 mg 3× daily (2.5-mg maximum group), or riociguat in individually-adjusted doses that were capped at 1.5 mg 3× daily (1.5-mg maximum group). Patients who were receiving no other treatment for PAH and patients who were receiving ERA or nonintravenous prostanoids were eligible. The primary endpoint was the change from baseline to the end of week 12 in 6MWD. By week 12, the 6MWD had increased by a mean of 30 m in the 2.5-mg maximum group and had decreased by a mean of 6 m in the placebo group (least-squares mean difference, 36 m; 95% CI: 20 to 52 m; $p < 0.001$). Oral riociguat therapy also improved hemodynamics, functional class, and time to clinical worsening. Subsequently, a subgroup analysis of patients with persistent/recurrent PAH after repair of CHD was performed on the datasets of the PATENT studies (83). Overall, 35 patients had persistent/recurrent PAH following complete repair of CHD in PATENT-1 (n = 12, 15, and 8 in the placebo, riociguat 2.5-mg maximum, and riociguat 1.5-mg maximum groups, respectively), and those patients recently underwent a subgroup analysis (83). Riociguat increased the mean 6MWD from baseline to week 12 by 39 ± 60 m in patients with PAH-CHD versus 0 ± 42 m for placebo. Riociguat also improved several secondary variables versus placebo, including PVR (−250 ± 410 vs. −66 ± 632 dyn·s/cm^5), NT-proBNP (−164 ± 317 vs. −46 ± 697 pg/ml), and WHO-FC (improved, stabilized, worsened: 21%, 79%, 0% vs. 8%, 83%, 8%, respectively). One patient in the riociguat 1.5-mg group experienced clinical worsening. Overall, riociguat was well tolerated (82–84). In the PATENT-2 extension (84), riociguat showed sustained efficacy and tolerability in patients with PAH-CHD at 2 years. The improvements in 6MWD, PVR, WHO-FC, and NT-proBNP in the PAH-CHD subgroup were consistent with the drug's effects in the entire study group of PATENT-1 (77). A RCT on the use of riociguat in children with PAH from 6 to 17 years of age is ongoing (PATENT-CHILD [Riociguat in Children With Pulmonary Arterial Hypertension (PAH)]; NCT02562235).

Selexipag is an orally-available selective prostacyclin receptor (IP receptor) agonist. Its high functional selectivity for the IP receptor may help minimize gastric side effects. In the large PAH, event-driven, randomized, double-blind, placebo-controlled, phase 3 trial on the efficacy of selexipag on the first morbidity and mortality event (GRIPHON [Selexipag (ACT-293987) in Pulmonary Arterial Hypertension]; n = 1,156) (85), selexipag significantly reduced the risk of morbidity/mortality events (composite primary endpoint: death from any cause or a complication related to PAH up to the end of the treatment period) versus placebo by 40% (HR: 0.60). Disease progression and hospitalization accounted for 81.9% of events. There was no significant difference in mortality between the 2 study groups. Oral selexipag may enable earlier combination drug therapy targeting the 3 molecular pathways of PAH by combining oral dosing with higher IP receptor selectivity. The first-in-child use of selexipag in PAH has recently been published (86), and an according drug trial is in preparation.

Because of the lack of any validated prospective pediatric data, or even drug approval for use in childhood, the previously mentioned compounds

macitentan, riociguat, and selexipag must be considered experimental pediatric PH pharmacotherapy ("compassionate use") until convincing, prospective clinical data become available.

Treatment algorithms on targeted PAH therapies are presented in **Figures 4 and 5**.

INTERVENTIONAL AND SURGICAL PROCEDURES (AS, REVERSE POTTS SHUNT, AND BILATERAL LUNG TRANSPLANTATION). Procedures for palliation of children with severe PAH and RV failure have been reported in which a right-to-left shunt is created with the aim of decompressing the right heart and increasing cardiac output (**Figure 4**). These interventions result in a hemodynamic situation that is similar to the physiology of ES patients, in whom RV systolic function is preserved longer and who have somewhat better survival than IPAH patients without a decompressing shunt. A detailed discussion of the indications and outcome of these interventions can be found elsewhere (58,87), and is outlined briefly in the following text.

Atrial septostomy. Atrial septostomy (AS) is a palliative therapy for patients with advanced PH and RV failure when medical therapy has failed (**Figure 4**). AS improves symptoms and quality of life in pediatric PAH, and may serve as a bridge to lung transplantation. Procedure-related mortality across centers worldwide was reported to be quite high (7.1% at 24 h and 14.8% at 1 month; median survival 60 months) (88); however, in expert centers and selected patients on PAH-targeted therapy, AS-related mortality was <1% (89,90). Lung transplantation-free and repeat AS-free survival at 30 days, 1 year, and 5 years was 87%, 61%, and 32%, respectively (90). Taken together, atrial septostomy can be considered in patients in WHO/NYHA functional class III and IV and with recurrent syncope despite combined medical therapy, and as a palliative bridge to transplant, increasing the chance for survival while waiting for a donor organ. Based on the risk factors found in the international study with high procedure-related mortality, *contraindications for AS* include: 1) mean RA pressure >20 mm Hg; 2) resting arterial oxygen saturation <90%; 3) severe RV failure; and 4) patients with impending death.

Reverse Potts shunt. This surgical procedure implies the construction of a connection between the left pulmonary artery (LPA) and the descending aorta (DAO), which allows right-to-left shunting. The use of a reverse Potts (LPA→DAO) shunt in suprasystemic PH is considered advantageous compared with atrial septostomy, as it provides highly oxygen-saturated blood for the coronary arteries and the central nervous system, only causes desaturation of the lower body, and additionally lowers the risk of fatal paradoxical embolisms. The reverse Potts shunt equalizes pulmonary arterial and aortic pressure, and pressure unloads the RV in systole, with a subsequent reduction in shifting of the interventricular septum toward the LV, and thus improvement in systolic and diastolic LV performance. The LPA-DAO shunt can be achieved either by a direct side-by-side anastomosis or by using a synthetic graft tube/prosthesis. Such a connection should be about the size of the DAO to allow sufficient decompression of the RV, whereas a runoff through the (then oversized) Potts shunt with decreased pulmonary perfusion, underfilling of the LV, extreme desaturation of the lower body, and subsequent undersupply of the myocardium and the brain should be avoided. Conversely, a Potts shunt should probably *not* be attempted in subsystemic PAH and/or end-stage RV failure, as the risk of very low cardiac output is high, or on patients who have not yet received any intravenous prostacyclin analogue. Considering that the experience with the Potts shunt procedure is nearly exclusively available in children, these data cannot be extrapolated to severely ill adults, who may have a considerably higher periprocedural risk (91). The Potts shunt procedure may be considered in patients with suprasystemic PH refractory to any medical treatment, including combined therapy (+ intravenous prostacyclin analogs) presenting in New York Heart Association/World Health Organization functional class III or IV.

The largest published series so far consists of 24 children with drug-refractory PAH in which a permanent Potts shunt was created (19 surgical LPA-DAO, 6 via stenting of a PDA) (92); 21 survivors showed persistent improvement in functional capacities without syncope or RV failure. Six patients experienced severe post-operative complications, and 3 early deaths related to low cardiac output occurred. After a mean follow-up of more than 2 years, the 21 survivors showed persistent improvement in functional capacities, and none of the patients had syncope or overt RV failure (92).

Several case series demonstrated the feasibility of the pure catheter-based interventional implementation of the LPA-DAO connection. The most elegant method is the implantation of a stent in a still-patent persistent ductus arteriosus (PDA). Ductal stenting is an established method in CHD with duct-dependent circulation, and can be established with considerably low periprocedural risk in experienced centers. The interventional de novo creation of a LPA-DAO connection with a covered stent from the LPA or DAO side was shown to be feasible (91,93) with good

pre-interventional CT imaging (94), but currently must be considered a high-risk procedure in end-stage patients with PAH who are too sick to undergo surgery.

Bilateral lung transplantation for end-stage PAH. Bilateral lung transplantation should be considered in children with inadequate clinical response on maximal combination therapy, including intravenous prostacyclin analogs, who remain in functional class III or IV. Mortality of children who are mechanically ventilated before transplantation is significantly increased (HR: 2.6). Due to long waiting times and influence on outcome, lung transplantation should be considered before cardiopulmonary decompensation has occurred. The median survival rate after lung transplantation in children is between 5.6 and 6.1 years (95). Details on indication and outcome of extracorporeal membrane oxygenation, ventricular assist device, and bilateral lung transplantation for end-stage PAH are discussed elsewhere (21,22,87,95).

TREATMENT OF PAH ASSOCIATED WITH CHD

BIVENTRICULAR CIRCULATIONS. Timely surgical repair is pivotal in correctable CHD, and corrective or palliative surgery is attempted mostly in the first 6 months of life to reduce pressure loads on the pulmonary vasculature. Still, PAH after surgical repair has been reported in 5.7% of adult patients with CHD. Of note, prognosis of post-operative PAH-CHD is similar to that of IPAH in children (1). However, there is no clear consensus on criteria for operability in left-to-right shunts with elevated PVR (**Figure 3**), nor is there a consensus on pre- and post-operative management of PAH in patients who do not meet operability criteria or who have persisting PAH after closure/correction of the defect (23).

"SIMPLE SHUNTS" (ASD, VSD, AND PDA). In simple shunts (ASD, VSD, PDA) (**Figure 3**) that are diagnosed in neonates/infants with clinical signs of heart failure and normal oxygen saturation, catheterization and AVT usually can be omitted before patients are referred for surgical shunt closure. Undiagnosed CHD that is asymptomatic for years and does not present with PAH until adulthood (e.g., ASD in the adult) represents a special entity, and cannot be compared to an ASD in childhood. For adult patients with pre-tricuspid shunts, complete assessment of pressures, oxygen transport and utilization, as well as the derived calculated variables is mandatory before considering surgery. A combination of pre- and post-capillary PH may be present, especially in the adult with chronic PH, which requires expert decision-making in terms of surgery or medical treatment. PAH-targeted pharmacotherapy before surgery may be indicated ("treat-to-close" concept) (**Figure 3**) (23).

In post-tricuspid shunts ("simple" VSD and PDA, or more complex CHD), early surgical repair of CHD (patch closure of the shunt or PDA ligation) within the first 2 years of life is essential to avoid irreversible changes to the pulmonary vasculature. In patients with an additional (genetic) risk for PHVD, particularly severe PHVD and/or post-operatively persistent PHVD, as in Down syndrome, surgical shunt closure should be performed within the first 6 months of life. These typical dates of surgery, indicating an optimal time frame to prevent persistent or progressive PAH-CHD, are well-accepted, and should eliminate at least the causative aspect of flow/shear-stress-related elevation of pulmonary pressures (23). Many pediatric PH centers would consider closing a post-tricuspid shunt (VSD, PDA) if the PVR index with vasodilator therapy is below 6 WU $\times$ m^2 and the PVR/SVR ratio is <0.3 (see "treat-to-close" concept, and "grey zone" in the CHD algorithm) (**Figure 3**) (23).

ADVANCED PAH-CHD AND ES. Patients with a CHD shunt may present beyond the optimal time point for surgery ($<$6 to 12 months of age), and either originate from countries with limited health care resources, or had the correct diagnosis missed in infancy. A complete evaluation of the pulmonary and systemic hemodynamics must be performed (2,25,27,30,31). If ES is already present, defect closure is associated with increased mortality and should not be pursued. Until now it has not been proven whether every patient with PAH-CHD, persistent post-tricuspid left-to-right shunt, and variable degree of PHVD-CHD necessarily develops ES. Although improved diagnostics and timely surgical-interventional treatment should make ES in CHD a rare entity, global (refugee) migration may lead to increasing numbers of PAH-CHD and ES patients in advanced health care systems worldwide.

MANAGEMENT OF POST-CAPILLARY PH. Valvular heart disease, such as mitral stenosis, may lead to post-capillary PH, which usually responds to surgical repair, whereas the reversibility of PH associated with restrictive LV physiology is less clear (e.g., CHD with small left-sided structures or adult heart failure with preserved ejection fraction). The evaluation of these patients should include a similar hemodynamic assessment (including acute vasoreactivity testing) as in PAH/PHVD-CHD.

SINGLE-VENTRICLE CIRCULATION. Patients with only 1 functional ventricle will ultimately undergo total cavopulmonary anastomosis (total cavopulmonary connection; Fontan procedure). Over time, these patients might develop heart failure due

TABLE 6 Characteristics of Small Studies and Randomized Trials in Fontan Patients With PAH-Targeted Drugs Interfering With the NO Pathway (Sildenafil), the Endothelin Pathway (Bosentan), and the Prostacyclin Pathway (Iloprost)

Drug(s) Tested	First Author, Year (Ref. #)	Patients (N)	Duration	Background Therapy	Primary Endpoint	Main Results
Sildenafil	Giardini et al., 2008 (99)	27	Single dose	No	VO_2 max	VO_2 max increased (single dose)
	Goldberg et al., 2011 (100)	28	6 weeks	No	VO_2 max	No difference in VO_2 max. at PE or AT Increased VE/CO_2 slope at AT
	Goldberg et al., 2012 (101)	27	6 weeks	No	VTI x HR	Trend to improved VTI × heart rate Improved MPI (Echo)
	Van de Bruaene et al., 2014 (102)	10	Single dose	No	CI and PVRi	Increased cardiac index (CMR) Increased SVI (CMR) Decreased PVRi at HIE (CMR)
Bosentan	Hebert et al., 2014 (103) (TEMPO RCT)	69	14 weeks	No	VO_2 max	Increased VO_2 max Increased exercise time Decreased NT-proBNP
	Schuuring et al., 2013 (104) (RCT)	32	6 months	No	VO_2 max	No difference in mean VO_2 max No difference in NT-proBNP
Iloprost (inhaled)	Rhodes et al., 2013 (105)	15	Single dose	No	O_2 pulse at PE	Increased VO_2 max Increased peak VO_2 pulse
Riociguat	–	–	–	–	–	Planned, no data available
Macitentan	–	–	–	–	–	Planned, no data available

Background therapy refers to PAH-targeted therapies, such as phosphodiesterase 5 inhibitors or endothelin receptor antagonists; patients received medications such as diuretic agents, angiotensin-converting enzyme inhibitors, beta-blockers, and antiarrhythmic agents.

6MWD = 6-min walk distance; AT = anaerobic threshold; CMR = cardiac magnetic resonance imaging; echo = echocardiography; HIE = high-intensity exercise; MPI = myocardial performance index (Tei); NO = nitric oxide; O_2 = oxygen; PE = peak exercise; peak VO_2 pulse = VO_2 max/heart rate (surrogate for stroke volume); PVR = pulmonary vascular resistance; RCT = randomized controlled trial; SVI = stroke volume index; TEMPO = Treatment With Endothelin Receptor Antagonist in Fontan Patients, a Randomized, Placebo-Controlled, Double-Blind Study Measuring Peak Oxygen Consumption; TTCW = time to clinical worsening; TT = treadmill test; VE/VCO_2 slope = ventilator inefficiency; VO_2 max = peak oxygen consumption; VTI = velocity time integral (VTI × heart rate = surrogate for stroke volume); other abbreviations as in Tables 1, 2, and 5.

to: 1) increased systemic vascular resistance, and predominantly post-capillary (secondary) PH and reduced oxygenation; 2) PHVD (pre-capillary) with a mean transpulmonary pressure gradient (mTPG) >6 mm Hg (PVRI definition, Panama, 2011 [13]); and/or 3) severe AV valve regurgitation, all of which affect ventricular contractility and stroke volume. Vasodilating drugs, such as ERAs (bosentan, macitentan), PDE5 inhibitors (sildenafil), and inhaled prostacyclin analogs (iloprost), have been used in Fontan patients with the goal of reducing both systemic vascular resistance and PVR, leading to decreased transpulmonary pressure gradient (TPG), increased pulmonary blood flow, and pressure unloading of the systemic ventricle. The clinical effects so far are promising, but somewhat ambiguous (**Table 6**) (96); however, a direct beneficial effect of the PDE5 inhibitors, ERAs, or the direct soluble guanylate cyclase stimulator riociguat on the ventricle (positive lusitropy and inotropy) has not been shown in studies of sufficient size.

FUTURE PERSPECTIVES

Further clinical and translational research is needed to optimize screening, diagnostics (including genetic testing), established therapies, and therapy tailored to treat the underlying pathological processes in the child/young adult with PH. Increasing evidence suggests that the RV and pulmonary arteries are equally important as therapeutic targets. RV maladaptation may include reactivation of fetal gene expression, induction of an epigenetic failure program, autonomic nervous system dysregulation, abnormal mitochondrial metabolism with inefficient adenosine triphosphate production, and reduced coronary artery perfusion with optional myocardial and microvascular injury (97). Future research should aim to modify, induce, or inhibit the underlying molecular targets. There are many additional challenges in pediatric PAH that need to be addressed and resolved in the future. First, randomized clinical trials need to be performed in the pediatric PAH population, although difficult regulatory requirements and inadequate clinical trial endpoints are severe obstacles (5). Valid, clinically-useful treatment goals need to be identified in pediatric PAH. These challenges require international, interdisciplinary PVD networks to conduct multicenter studies and to establish high quality, open pediatric PH registries.

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