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Pediatric Pulmonary Hypertension: Definitions, Mechanisms, Diagnosis, and Treatment

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Abstract

Pediatric pulmonary hypertension (PPH) is a multifactorial disease with diverse etiologies and presenting features. Pulmonary hypertension (PH), defined as elevated pulmonary artery pressure, is the presenting feature for several pulmonary vascular diseases. It is often a hidden component of other lung diseases, such as cystic fibrosis and bronchopulmonary dysplasia. Alterations in lung development and genetic conditions are an important contributor to pediatric pulmonary hypertensive disease, which is a distinct entity from adult PH. Many of the causes of pediatric PH have prenatal onset with altered lung development due to maternal and fetal conditions. Since lung growth is altered in several conditions that lead to PPH, therapy for PPH includes both pulmonary vasodilators and strategies to restore lung growth. These strategies include optimal alveolar recruitment, maintaining physiologic blood gas tension, nutritional support, and addressing contributing factors, such as airway disease and gastroesophageal reflux. The outcome for infants and children with PH is highly variable and largely dependent on the underlying cause. The best outcomes are for neonates with persistent pulmonary hypertension (PPHN) and reversible lung diseases, while some genetic conditions such as alveolar capillary dysplasia are lethal.

Introduction

Pediatric pulmonary hypertension (PPH) comprises a variety of etiologies spread across the entire age spectrum from newborn to late adolescence. PH is defined as the elevation of pulmonary arterial pressure (PAP) and is commonly diagnosed by echocardiography or cardiac catheterization after it becomes clinically apparent. Use of specific terminology is important to describe PH, which refers to elevated PAP from any cause. Pulmonary arterial hypertension (PAH) refers to precapillary PH with normal or low pulmonary capillary wedge pressure (see below for definition). The major types of PH that occur in the pediatric age group are persistent pulmonary hypertension of the newborn (PPHN), which is classified as 1.7 in current Nice classification, congenital heart disease (CHD) (1.4.4), developmental lung diseases (3.5), and idiopathic pulmonary arterial hypertension (IPAH) (1.1). PPHN has a different etiology, presentation, and clinical course compared to other causes of PPH; a vast majority of affected neonates recover without sequelae. PPH associated with developmental disorders of the lung such as bronchopulmonary dysplasia (BPD) and congenital diaphragmatic hernia (CDH) and PH associated with CHD are important causes

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of long-term PH in children. It is increasingly being recognized that pediatric PH is different from adult PH, in etiology, clinical presentation, and outcomes. The 6th World Symposium on Pulmonary Hypertension (WSPH) published new definitions and classifications for PH in 2018, which are reflected in this article. Mechanisms of PH usually involve an imbalance between the vasoconstrictor and vasodilator forces in the pulmonary vasculature, which leads to elevated pulmonary vascular resistance (PVR), which in turn leads to increased right ventricular afterload and eventual right ventricular failure. PPH, with or without temporal association with elevated PA pressure, is usually due to disruption of normal development. Therapies to treat PH aim to treat this imbalance and decrease RV afterload and increase cardiac output. PH can occur secondary to three distinct mechanisms: pulmonary vasoconstriction, which is responsive to vasodilator therapy, vascular remodeling with thickening of media and adventitia of affected vessels, and a decrease in angiogenesis with pruning of the vascular tree (Figure 2).

Definition

The PAP is equal to the systemic pressure *in utero* and decreases after birth due to a decline in the PVR, reaching adult levels by 2 to 3 months of age. PH has been traditionally defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg, while the term PAH refers to elevated PAP with a pulmonary artery wedge pressure ≤15 mmHg in adults, children and term infants >3 months of age at sea level since the 1st WSPH in Geneva in 1973 (4, 38). The criteria for infants and children also include indexed pulmonary vascular resistance (PVRI) as certain classes of pediatric PH cannot be defined with mPAP alone. Children with left-to-right shunts (aortopulmonary or intracardiac shunts) with increased pulmonary blood flow may not have pulmonary hypertensive vascular disease (PHVD) early on, even though they have increased mPAP. Conversely, children without a subpulmonary ventricle might have PHVD even with an mPAP <25 mmHg. Therefore, it was recommended that a PVRI > 3 Wood units (Wu)/M^2 be used to define PHVD. The recent 6th WSPH in Nice, France, in 2018 decreased the lower limit for mPAP for adult PH to >20 mmHg to include cases of precapillary PH, as long as PVRI > 3 Wood units (Wu)/M^2 based on data showing even mildly elevated mPAP of 21 to 24 mmHg to be an independent predictor of worse outcomes in adult PH and right heart catheterization studies in healthy normal adults demonstrating mPAP of ~14 ± 3.3 mmHg at rest (192, 319, 375, 544). Following this recommendation, the Pediatric Task Force of the 6th WSPH also modified the criteria for diagnosis of pediatric PH to mPAP > 20 mmHg after three months of life, or PVRI ≥ 3 Wu/M^2 (506). Table 1 is a comprehensive clinical definition of pediatric PH adapted from the European Pediatric Pulmonary Vascular Disease Network (EPPVDN) modeled on the 6th WSPH definitions.

Epidemiology

Comprehensive data on national incidences of PAH in the neonatal and pediatric population are lacking. A recent large-scale insurance claim-based study of pediatric PAH in the United States found an incidence of 4.8 to 8.1 per million children per year and a prevalence of 25.7 to 32.6 per million children (349). The first multinational registry in pediatric pulmonary hypertension (PH) is the Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry, which includes data from 31 centers in 19 countries, although

they do not report incidence or prevalence data (69). In the TOPP registry, a majority of patients (88%) had PAH, which was primarily IPAH, heritable pulmonary arterial hypertension (HPAH), or PAH associated with congenital heart disease (CHD-PAH); 12% of these patients had PH due to lung disease, with BPD being the most common cause. Another large-scale registry in the United States is the combined adult and pediatric observational cohort, Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). In this cohort, 56% of the children had IPAH/HPAH and 36% had CHD-PAH (58). This is different from the adult data from the same registry where only 12% had CHD-PAH but 24% had PAH associated with connective tissue diseases (CTDs) such as scleroderma (68). 73% of the pediatric cohort had a World Health Organization Functional Class (WHO-FC) I or II at the time of enrolment, whereas 53.7% of the adults were already at WHO-FC III or IV at the same time. Five-year survival for children with PAH was ~75%, with older age being associated with decreased odds of survival. A Netherlands registry-based study reported a yearly incidence of 63.7 cases per million children, with over 80% of these cases being transient PAH (604). The reported incidence and point prevalence of sustained PAH in this Dutch registry were 3 per million children per year and 20 per million children, respectively. A Spanish registry-based study reported an incidence of 4 per million children per year and a prevalence of 20 cases per million children, after excluding transient forms of PH (142).

This data is like the US data, which also excluded transient and early forms of PH such as PPHN and postoperative PH. Data from the UK Service for PH in Children for only IPAH revealed an incidence of 0.48 per million children per year and a prevalence of 2.1 per million children, which are similar to that of other registries (401). BPD, which is the most common morbidity in the preterm infant population, is associated with PH, which increases with increasing BPD severity with numbers of 6%, 12%, and 39% in mild, moderate, and severe BPD reported in a meta-analysis; single-center cohort studies reported the prevalence of BPD-PH to be between 15% and 64% in preterm infants with severe BPD (29, 419, 630). PPHN is the most common cause of transient PAH with an incidence of ~1.9 per 1000 births (613).

Classification of PH with the Most Recent Changes Approved at Nice Conference, 2018

Pulmonary hypertensive diseases were first classified in 1998 at the WSPH in Evian, France (542), and since then have been revised several times. The first Pediatric Task Force of the WSPH met at the 5th WSPH in Nice, France, in 2013 and concluded that a common classification for pediatric and adult PH is preferred as more children with PH are now surviving into adulthood and it is important to share a common language for the purpose of definition and classification (543). The Pediatric Task Force of the 6th WSPH in 2018 proposed some changes that are reflected in the new classification (Table 2) and are more representative of the changing landscape of pediatric PH (506). The four major changes and rationale behind the changes are summarized below:

I. A new class was added to Group 1 PH called PAH long-term responders to calcium channel blockers (CCBs) (Group 1.5), which is similar to adults with

PAH who respond positively to an acute vasoreactivity test (AVT). Based on the criteria used (Sitbon vs modified Barst), the percentage of children with PAH who have a positive AVT ranges between 15% and 30% (157, 548).

II. Dutch registry-based data had shown that among children with nontransient PH, a significant proportion (34%) had PH associated with developmental lung diseases such as BPD, CDH, and congenital pulmonary vascular abnormalities (604). Hence, Group 3.5 was dedicated to developmental lung diseases, which also includes a growing list of genetic developmental lung disorders such as surfactant protein deficiency and alveolar capillary dysplasia (ACD).

III. Children with single-ventricle physiology may have increased or decreased pulmonary blood flow at various stages and hence do not always fit the classic definition of mPAP > 25mmHg, but they develop PHVD that markedly impairs survival and outcomes. Hence, the 6th WSPH Pediatric Task Force has grouped PHVD in the setting of single-ventricle physiology in Group 5.4.

IV. The Task Force also agreed that Down syndrome-associated PH is variable and does not fit into a single universal classification group and hence will be classified as Group 3 PH unless they have CHD (506).

The contribution of various classes of PH under Nice classification as they apply to pediatric PHVD is described in more detail below. Specific differences between adult and pediatric PH under these categories are discussed. Table 3 discusses the clinical features, hemodynamic findings, and treatment strategies of some of the most common forms of pediatric PHD.

Group 1 PH (pulmonary arterial hypertension)

1.1 Idiopathic PAH (IPAH):

IPAH is defined as PAH without any identifiable cause that leads to gradual pulmonary vascular remodeling, which includes adventitial thickening, medial hypertrophy, intimal proliferation, and formation of concentric laminar intimal fibrosis and plexiform lesions. This causes vascular wall thickening and occlusion of small pulmonary arteries, which combined with vasoconstriction, inflammation, and thrombosis increases PVR and pressure. This leads to increased right ventricular afterload and eventual right heart failure and death (262, 277). Estimated incidence rates for IPAH range from 0.47 to 1-2 cases per million children, with estimated prevalence rates varying from 2.1 to 4.4 cases per million children (4). Up to 25% of patients with IPAH have mutations in genes linked to HPAH; these genes are listed under that category. Based on these observations, evaluation of IPAH patients should include genetic screening for known mutations in common genes linked to PAH (233).

1.2 Hereditary PAH (HPAH):

Multiple genetic mutations have been identified in the pediatric PAH population and are implicated in 20% to 30% of sporadic PAH and almost 80% of familial PAH (4). Bone morphogenetic protein receptor type 2 (BMPR2) is the gene most implicated in HPAH, with

studies finding ~55% in familial PAH and ~10% in IPAH in both adult and pediatric PAH patients (470, 508, 659). Children and adults with BMPR2 mutations who present with PAH are more likely to have worse disease at diagnosis, present at a younger age, are less likely to respond to AVT, and are at an increased risk of death and/or transplantation (165, 508). Recently, TBX4 gene mutations that cause small-patella syndrome have been implicated in pediatric HPAH (295). Two cohort-based genetic studies found that TBX4 mutations were more enriched in the pediatric PAH population compared to adults (10/130 pediatric vs 0/178 adult onset), and TBX4 gene variant carriers had younger age of disease onset compared to BMPR2 gene variant carriers (347, 659). ACVRL1 mutations have also been implicated in pediatric HPAH, with increased enrichment compared to the adult population (188, 347, 508). Current European Pediatric Pulmonary Vascular Disease Network (PPVDN) and the 6th WSPH Pediatric Task Force recommendations are to offer genetic counseling to all families with children diagnosed with IPAH/HPAH and to evaluate family members of known mutation carriers for PAH if they develop any new cardiorespiratory symptoms (235).

1.3 Drug- and toxin-mediated PAH:

Diazoxide, which is used for the treatment of hyperinsulinemic hypoglycemia in the neonatal population, has been linked to transient PAH that resolves after discontinuation of the drug (385). Neonates on diazoxide should be evaluated for PAH if they develop symptoms of respiratory distress or poor feeding. The illicit use of methamphetamine, a drug used to treat neuropsychiatric disorders, has been linked to PAH—methamphetamine-associated PAH (meth-APAH). Meth-APAH presents with a more severe form of disease, poorer long-term outcomes, and prognosis compared to IPAH (652). Methamphetamine metabolites accumulate within the lung, leading to toxicity and vascular damage (612). PAH patients should be screened for a history of drug use, and, conversely, methamphetamine users should undergo screening for signs and symptoms of PAH (115, 489).

1.4 1.4.1 PAH-CTD:

PAH can be a rare complication of CTD and has mostly been described among patients with systemic sclerosis (SSc), with an estimated prevalence of 5% to 10% (574, 606). It is also a rare manifestation of systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), dermatomyositis, polymyositis, Sjogren's syndrome, and rheumatoid arthritis (89, 236, 280, 323, 487). CTD-associated PAH usually carries a worse prognosis compared to IPAH (517). In general, PH associated with CTD, HIV, and portal hypertension is less common in pediatric compared to adult population (171).

1.4.2 HIV-associated PAH: As mortality from HIV has decreased, the incidence of cardiovascular diseases due to antiretroviral treatment-associated dyslipidemias and insulin effects as well as HIV-induced chronic endothelial dysfunction, impaired fibrinolysis and chronic inflammation have increased (287). HIV patients are seven times more likely to develop PAH than the rest of the population. The incidence of PAH varies anywhere between 10% and 50% in adult patients with HIV (45, 259, 403), although less common in pediatric population.

1.4.3 PAH associated with portal hypertension: This can be of two distinct subtypes—hepatopulmonary syndrome (HPS), which is characterized by low PVR and increased pulmonary blood flow, and porto-pulmonary hypertension (POPH), which is characterized by increased pulmonary vascular remodeling and elevated PVR.

1.4.4 PAH-CHD: This includes all forms of PAH associated with CHD, except complex CHDs (Group 5.4 described later) as well as PAH secondary to Eisenmenger's syndrome in those with left-to-right shunts. Although adults with PAH and Eisenmenger's syndrome have better mortality rates than IPAH/HPAH, for children the survival for PAH-CHD and IPAH/HPAH are similar (29% vs 25%) (58). PAH-CHD is associated with a pre- or post-tricuspid shunt lesion with or without pulmonary vascular disease and distinct patterns of right ventricular hypertrophy (RVH). Post-tricuspid lesions are left-to-right shunts (ventricular septal defects for example) that expose pulmonary circulation to systemic pressure and cause LV volume overload, leading to both volume/pressure overload on the pulmonary circulation. Untreated, most of these patients will develop Eisenmenger's syndrome with a reversal of the shunt direction to right-to-left due to gradual progression of pulmonary pressures to a supra-systemic level (454). Pre-tricuspid lesions like atrial septal defects can be left-to-right or sometimes bidirectional. They are usually slow to progress to florid PAH due to low atrial pressures and rarely develop Eisenmenger physiology. The prognosis of these lesions is excellent if repaired early in life. PAH-CHD not associated with shunt physiology is encountered after cardiac surgery of some cardiac defects such as transposition of great vessels (TGA, transposition of great arteries), truncus arteriosus (TA), Tetralogy of Fallot (TOF), double-outlet LV, pulmonary atresia/intact ventricular septum, and aortopulmonary septal defect. It should be noted that prognosis for PAH-CHD is significantly worse for children with CHD in resource-constrained areas of the world where surgical correction is delayed, perioperative management is variable, and PHD becomes established, leading to a higher mortality risk. PAH can also develop in the setting of single-ventricle physiology. Bidirectional Glenn shunts and Fontan baffles are often used in children whose CHD precludes a direct repair due to hypoplastic ventricle. This leads to systemic venous blood draining directly into the pulmonary arteries, and there is no dedicated subpulmonary ventricle. This can lead to elevated PVR, which affects operability and outcomes of these patients with cavopulmonary anastomoses (200, 362, 397). Children can develop pulmonary arteriovenous fistulae after Glenn procedure, where only the superior vena cava blood flows into the lungs while the inferior vena cava blood bypasses the lungs to enter the systemic circulation directly. Although loss of hepatic venous blood drainage to the lungs has been suspected as being involved in the AV fistula development, cellular mechanism for AV fistula formation in this setting remains unknown. Both bosentan and sildenafil have been used in patients after Fontan repair to improve hemodynamics and oxygen consumption (212, 455).

1.4.5 Schistosomiasis: It is a rare entity in the developed world and found more commonly in countries with endemic schistosomiasis. Globally, this is one of the most common causes of PAH, with 5% of patients with hepatosplenic schistosomiasis developing PAH.

1.5 PAH long-term responders to CCBs:

A subset of pediatric PAH patients have positive AVT to oxygen and/or inhaled nitric oxide (NO) based on Sitbon or modified Barst criteria and respond to oral calcium channel blockers (CCBs) with decreased pulmonary pressures. These children account for ~ 8% to 15% of all pediatric IPAH patients when using Sitbon criteria (548).

1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement:

Pulmonary venous obstructive disease (PVOD) or pulmonary capillary hemangiomatosis (PCH) is rare in children. Biallelic mutations in the *EIF2AK4* gene have been implicated in heritable cases of both PVOD and PCH (7, 78, 166). Risk factors for nonidiopathic PVOD include chemotherapy, organic solvent or tobacco exposure, autoimmunity, and inflammatory conditions (233, 405). The incidence of PVOD/PCH is estimated to be ~0.7% to 2% of all PAH cases (506).

1.7 Persistent pulmonary hypertension of the newborn (PPHN):

Estimated at 30.1 cases per million children per year, this is the most common cause of transient PAH. The fetal lung circulation receives 13% to 21% of cardiac output as the placenta is the site for gas exchange (495). After birth there is an eightfold increase in the pulmonary blood flow due to a drop in the PVR mediated by increased oxygen tension, ventilation, shear stress, and increased vasodilatory molecules such as NO and prostacyclin (PGI2) (326). PPHN occurs when one or more of these mechanisms fail to lower the PVR, which leads to extrapulmonary shunting of deoxygenated blood from right-to-left through the patent ductus arteriosus (PDA) and/or patent foramen ovale (PFO) with profound systemic hypoxemia, differential oxygen saturation gradient between the pre- and postductal circulation and increased risk of death or neurodevelopmental impairment in survivors (190, 312, 315). PPHN can be due to (i) increased pulmonary vasoconstriction in the setting of a structurally normal architecture, which is seen in lung parenchymal diseases like meconium aspiration syndrome, respiratory distress syndrome, sepsis, and pneumonia; (ii) pulmonary vascular remodeling and altered vasoreactivity and impaired angiogenesis seen in idiopathic PPHN; and (iii) pulmonary hypoplasia leading to hypoplastic pulmonary vasculature seen in CDH and maternal oligohydramnios (190). The prevalence of PPHN has been historically described as 1.9 per 1000 births; however, with growing recognition of the syndrome especially in preterm infants, the numbers have been rising (613). In addition to the conditions described, other risk factors for developing PPHN include maternal use of selective serotonin reuptake inhibitors (SSRIs) or nonsteroidal anti-inflammatory drugs (NSAIDs), prematurity, male gender, maternal diabetes, asthma, and obesity (143, 245, 423). Mortality for PPHN was >50% prior to extracorporeal membrane oxygenation (ECMO) and use of pulmonary vasodilators like inhaled nitric oxide (iNO). Although mortality rates have decreased to less than 10%, long-term adverse outcomes like cerebral palsy, deafness, and blindness remain high in survivors (317).

Group 2

PH due to left heart disease (LH disease): LH disease is gradually being recognized as an important contributor to pediatric PH. Repair of CHD like coarctation of aorta, VSD, mitral

valve replacement, hypoplastic left heart syndrome, and cardiac transplantation can 6lead to left ventricular dysfunction, thereby causing increased back pressure in the pulmonary venous circulation and ultimately postcapillary PH. LV dysfunction is also increasingly being recognized as a cause of BPD-PH (320). Valvular lesions like mitral or aortic stenosis (AS) can also lead to a similar feature of increased pressure in the pulmonary capillary bed. Critical AS or aortic atresia in fetuses and newborns is associated with increased pulmonary vascular muscularization, and pulmonary veins become arterialized *in utero*, leading to impaired postnatal pulmonary vascular adaptation (241). Outcome for these infants has improved and 5-year survival rates are between 77% and 85% at 5 years (199). Pulmonary vein stenosis (PVS) is associated with very high mortality rates and worse outcomes; medical or surgical therapies are mostly ineffective (609, 649). Like LV dysfunction, this is also becoming an increasing feature in BPD-PH and contributes to increased mortality in this population (320).

Group 3

PH due to lung diseases and/or hypoxemia: Interstitial or parenchymal lung diseases or systemic diseases that affect ventilation of the lung cause chronic hypoxia, which leads to pulmonary vasoconstriction, pulmonary vascular remodeling, and ultimately right heart failure to high afterload. This includes chronic hypoventilation and obstructive sleep apnea (OSA) as well hypobaric hypoxia resulting from high altitudes. OSA in otherwise normal children with enlarged tonsils and adenoids showed almost 20% incidence of RVH by echocardiography and 37% of children with OSA diagnosed on sleep study have decreased RV ejection fraction measured by radionuclide ventriculography (336, 582).

BPD-associated pulmonary hypertension (BPD-PH):

Altered lung development due to growth arrest of alveoli and pulmonary capillaries can lead to the vascular phenotype of BPD-PH (75). Pathogenesis of BPD-PH is multifactorial as shown in Figure 1. Maternal factors such as chorioamnionitis, smoking, preeclampsia, and intrauterine growth restriction, especially if accompanied with reversed or absent end-diastolic flow in the umbilical arteries, are prominent risk factors for BPD-PH in a growing population of extremely preterm infants (75, 114, 387). Small-for-gestational age (SGA) is another risk factor for PH in preterm infants with and without BPD (29). Postnatal lung injury from ventilation and oxygen exposure, infections, inflammatory response, and poor postnatal growth together contribute to alveolar and vascular injury and growth arrest. Two other morbidities associated with prematurity—necrotizing enterocolitis (NEC) and retinopathy of prematurity (ROP)—were also strongly associated with the increased prevalence (29) of BPD-PH in a cohort study from the Children's Hospital Neonatal Consortium. This study also reported the incidence of PH in preterm infants <32 weeks gestational age with severe BPD to be at 22% (325). During admission, PH was associated with increased mortality and duration of ventilation and after discharge with medical interventions, including tracheostomy, supplemental oxygen use, tube feeds, and increased frequency of readmission through 1 year of life. Presence of PH is strongly associated with increased mortality with reports ranging from 14% to 38% and a meta-analysis reporting 16% mortality before discharge and 40% at two years of life (29, 75). The prevalence of PH

increases in step with BPD severity. A meta-analysis and single-center cohort studies reported numbers of 6%, 12%, and 39% in mild, moderate, and severe BPD and the prevalence of BPD-PH to be between 15% and 64% in preterm infants with severe BPD (29, 419, 630). BPD is associated with dysmorphic growth of pulmonary vessels, reduced microcirculation, and altered distribution of vessels. This abnormal vasculature contributes to impaired alveolar-capillary gas exchange causing prolonged hypoxemia, requirement for positive pressure ventilation, and the risk of developing severe PH (2, 18, 139, 588). The pulmonary vasculature shows increased tone and vasoreactivity, decreased growth and increased hypertensive remodeling. This leads to high resting PVR even in the absence of hypoxia and an exaggerated pulmonary vasoconstrictor response to hypoxia. Decreased growth and pruning of vessels lead to severely compromised lung perfusion and right heart strain, especially if significant left-right shunts (8, 79, 416, 417, are, present). Development of pulmonary vascular disease early on in the course of life also strongly correlates with increased severity of BPD, which is an independent risk factor for the development of late BPD-PH (419). Three additional findings on echocardiogram for these preterm infants are being increasingly recognized as contributory and prognostic factors for the development and outcome of BPD-PH—PVS, left ventricular dysfunction, and presence of aortopulmonary collaterals. The prevalence of PVS in a cohort of infants with BPD-PH who underwent cardiac catheterization was 26%, and there have been reports of association with NEC (141, 243, 370, 575). Left ventricular diastolic dysfunction should be suspected in the setting of PH with worsening pulmonary edema or increasing diuretic requirements.

Congenital diaphragmatic hernia-associated pulmonary hypertension (CDH-PH):

CDH is a birth defect characterized by the herniation of intra-abdominal contents into the thoracic hernia through a diaphragmatic defect *in utero*. This is a life-threatening condition resulting in death if not medically managed and surgically corrected. With the advent of antenatal diagnosis, better surgical techniques, ventilatory management, and ECMO support, the mortality has decreased to 25% to 30% in the last few decades. The incidence of CDH is ~1 in every 2500 births and PH occurs in nearly 60% to 70% of these infants (266, 556). PH persisting to 1 month of age in CDH is strongly associated with increased mortality (~45%). A multicenter cohort study reported only a 43.9% survival rate when the ratio of RV to systemic pressure at 1 month was greater than 0.67 and 98.6% survival when the ratio was <0.5 (635). The two-hit hypothesis for CDH-PH proposes an early embryonic alteration of the pulmonary vasculature and parenchymal development followed by a later mechanical compression by the herniated abdominal contents leading to pulmonary hypoplasia (292). This leads to a hypoplastic pulmonary vascular bed with decreased arborization and altered vasoreactivity along with increased remodeling with medial and adventitial thickening (239, 400). Left ventricular hypoplasia and dysfunction due to altered mechanics of the thoracic cavity add to this by causing pulmonary venous hypertension (539). LV mass was significantly smaller in nonsurviving infants with CDH, which could be due to compression by the abdominal contents, redistribution of fetal cardiac output from LV to RV in CDH, or less pulmonary venous return to the left side of the heart from the hypoplastic CDH lung (302). This is an important factor contributing to the success or failure of pulmonary vasodilators in the treatment of acute or postoperative PH in the CDH, as they may

contribute to worsening wedge pressure and pulmonary edema in the presence of LV dysfunction (359).

ACD with misaligned pulmonary veins is a uniformly fatal disorder characterized by immature lobular development, abnormal air-blood barrier, and an underdeveloped pulmonary capillary bed (81). Mutations in FOXF1 gene are found in 40% to 60% of infants with ACD, particularly in the presence of coexisting anomalies such as anorectal malformations, skeletal defects, and congenital heart defects (576). Most cases of ACD develop severe PAH and die despite maximal PH therapy.

Group 4: PH due to pulmonary artery obstruction

4.1 Chronic thromboembolic PH (CTEPH) occurs in 0.5% to 3.8% of patients with acute or recurrent pulmonary thromboembolism (394). The embolus transforms into a fibrotic residue, resulting in proximal vessel obstruction and distal arteriopathy leading to PH and right ventricular failure (414). CTEPH should be considered in all symptomatic pediatric patients with known hypercoagulable state, history of thromboembolism, or venous catheter placement, especially as the rate of venous thromboembolism in the pediatric population has been rising (488). Pulmonary thromboendarterectomy (PTE), which involves removal of organized thromboembolic material from the vessel intima, is usually well tolerated in these patients with improved hemodynamic and functional status and low perioperative mortality (127, 368).

The illness caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), better known as COVID-19 (coronavirus disease-19), also leads to a coagulopathic state causing venous thromboembolic events. Autopsies of patients who died from COVID-19-induced acute lung injury (ALI) show damage to the pulmonary vascular endothelium and pulmonary capillaries filled with dense fibrin-rich microthrombi (10, 398). Although cases of CTEPH have not been reported in the pediatric population from COVID-19 sequelae, having a follow-up strategy for identifying residual clot burden and potential hemodynamic consequences is important in this group (150). An adult cohort study of right heart catheterization data in mechanically ventilated COVID-19 patients comparing it to patients with acute respiratory distress syndrome (ARDS) from non-COVID-19 causes found that although PVR was lower in COVID-19, there was a high incidence of PH in COVID-19, with a majority being postcapillary PH (101).

Table 4 discusses the key differences between precapillary, postcapillary, and a mixed type of PH in the pediatric population.

Another clinical classification described in this article is the 2011 Panama classification for pediatric PH (Table 5). This is different from the WSPH classification, which has often been critiqued as more adult PH-oriented. The Panama classification was proposed by the Pulmonary Vascular Research Institute (PVRI) Pediatric Taskforce, which was a group of North and South American pediatric PH experts (328).

Functional classification

Functional classification (FC) of PH is difficult in infants and children due to the practical difficulty of performing exercise tests and the lack of reliable self-reporting of symptoms. The New York Heart Association (NYHA) FC is commonly used by cardiologists to assess clinical status in adults with heart failure. The WHO-FC is a FC for adults with PH, which is modeled on the NYHA FC (26).

WHO-FC:

Class I: Patients with PH but without limitation of physical activity. Ordinary physical activity does not cause undue dyspnea, fatigue, chest pain, or near syncope.

Class II: Patients with PH resulting in slight limitation of physical activity, comfortable at rest. Ordinary physical activity causes undue dyspnea, fatigue, chest pain, or near syncope.

Class III: Patients with PH resulting in marked limitation of physical activity, but comfortable at rest. Less than ordinary physical activity causes undue dyspnea, fatigue, chest pain, or near syncope.

Class IV: Patients with PH resulting in inability to carry out physical activity without symptoms. Symptoms of right heart failure are present, and dyspnea and fatigue are usually present at rest. Syncope or near-syncope may occur.

The Pediatric Task Force of the PVRI proposed a new FC for PH in children in 2011 (Table 6), known as the Panama classification (328). This is stratified into five different classes based on the ages of 0 to 0.5 year, 0.5 to 1 year, 1 to 2 years, 2 to 5 years, and 5 to 16 years. After 16 years, adult FCs can be reliably used. These incorporate weight gain and developmental milestones into the assessment along with increased self-reporting of symptoms as the child grows older.

Cellular and Structural Changes

A variety of cellular and structural changes play a complex role in the pathogenesis of PH (see Figure 2). The primary imbalance between the vasoconstrictor and vasodilator pathways leads to persistent vasoconstriction and pulmonary vascular remodeling, eventually causing right ventricular failure secondary to increased afterload. Alterations in cell biology are presented below for each vascular cell; however, the cell-cell communications are integrated into a complex signaling network that affects the entire vascular wall.

Endothelial cells

The innermost layer of blood vessels is composed of a monolayer of endothelial cells supported by an internal elastic lamina. This endothelium forms a nonthrombogenic, semipermeable barrier between the bloodstream and the extravascular tissues. It regulates vascular tone, hemostasis, growth and differentiation of blood vessels as well as chemotaxis (466). Endothelial cells are the first cells to be exposed to the effects of low oxygen tension in the blood. Chronic hypoxia leads to endothelial cell hypertrophy, as evidenced by the

increased DNA synthesis and increased cell number, which are demonstrated by an approximately threefold increase in ^{3}H-thymidine incorporation by endothelial cells early during hypoxia exposure. Endothelial cells undergo disorganized proliferation, which could lead to plexiform lesions or concentric obstructive lesions, both of which lead to obliteration of the pulmonary vascular lumen (596). Plexiform lesions are glomeruloid-like disorganized endothelial cells, which demonstrate markers of angiogenesis such as HIF-1α and VEGF (597). They are most commonly found in IPAH and Group 2 PH. Concentric lesions are onionskin-like proliferative growth of endothelial and/or smooth muscle cells. Rarely, paucicellular lesions can be found in the intima of the pulmonary hypertensive artery, which is characterized by increased extracellular matrix (ECM) and mucopolysaccharides and decreased endothelial cell number (596). The intimal fractional thickness, which is a measure of the contribution of the intima to the overall diameter, shows an almost threefold increase in patients with severe PAH (561). The subendothelial space, which is present between the endothelial cell and its basement membrane, contains increased amounts of collagen, elastin, and microfibrils in autopsy specimens of infants dying from PH. Endothelial cell elastin production, which is suppressed in late fetal and early neonatal life, is upregulated by reexpression of tropoelastin mRNA in endothelial cells in response to hypoxic injury (161, 566). Hypoxia leads to increased expression of neutrophil chemotactic factors on endothelial cells (391). Endothelial cells release mediators that regulate vascular tone and smooth muscle proliferation, and the balance between vasodilatory and vasoconstrictive mediators is lost in PH. The three principal mediators are NO, PGI_2, and endothelin (ET-1), which are described in detail in Section 6 in this article.

Smooth muscle cells (SMCs)

SMCs play one of the most important roles in increased pulmonary vascular contractility, increased muscularization of the resistance arteries, medial thickening, abnormal muscularization of the distal nonmuscular pulmonary arteries, and increased ECM production leading to pulmonary vascular remodeling. Pulmonary artery smooth muscle cells (PASMCs), which are in a quiescent state of performing contractile function during the normal physiological state, possess a unique feature unlike other vascular SMCs—they are not terminally differentiated and hence can modulate their phenotype greatly in response to stress and changes in their environment (577). The key processes that change SMC phenotype in response to a PH-causing environment are hypertrophy, proliferation or hyperplasia, resistance to apoptosis, and migration. SMC hypertrophy occurs mainly from increased protein synthesis with decreased breakdown, along with the increased intracellular water content (73). There is increased expression of Na^+ ion channels, which are key to the maintenance of increased cell volume. This hypertrophy is also mediated by G-protein-coupled receptor-agonists such as angiotensin II (ANGII), ET-1, thromboxane-A2 (TXA2), and other receptor tyrosine kinases. SMC proliferation, which contributes to the medial thickness and the muscularization of nonmuscular arteries, is regulated by increased Ca^{2+} levels. There are conflicting reports as to whether hypoxia directly exerts a mitogenic effect on PASMCs, whether hypoxia stimulates the PASMCs to produce an autocrine growth factor, or whether hypoxic stimulation leads to the synthesis of paracrine signals from the neighboring PAECs, which result in PASMC proliferation. PH leads to upregulation of transient receptor potential channel (TRPC) genes and store operated Ca^{2+} entry (SOCE)

channels, which result in increased cytosolic Ca^{2+} concentration. Ca^{2+} binds to calmodulin, which activates Ca^{2+}-calmodulin-dependent protein kinases, which in turn phosphorylate transcription factors such as Ca^{2+}/cAMP-response element binding protein (CREB) and Ras, responsible for initiating and maintaining the cell cycle (331). PASMC proliferation has also been linked to the activation of the mTOR pathway, and rapamycin (mTOR inhibitor) normalizes the growth of PASMCs in the monocrotaline (MCT)-induced PH model (258). NO donors were found to inhibit hypoxic PASMC proliferation *in vitro* in a dose-dependent manner with associated cGMP increases (20). PASMC migration is a phenomenon that occurs during development, vascular injury, and vessel wall remodeling. Growth factors like platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (FGF2), as well as cytokines like IL-6, have all been implicated in increased PASMC migration (202).

Role of fibroblasts and extracellular matrix

Monocytes, macrophages, T lymphocytes, and dendritic cells have all been found in the plexiform and other lesions of PAH-affected human lungs (600). Fibroblasts are the major cell type found in the adventitial layer of the pulmonary vasculature and produce ECM and matricellular proteins (569). They are often the first cells to become activated, proliferate, and differentiate in response to injury (372). In addition, PAH is characterized by endothelial-to-mesenchymal transformation (EndMT) where PAECs lose their cell-to-cell connections due to loss of cell surface markers, detach from the endothelial monolayer, migrate to the medial layer, and dedifferentiate into myofibroblast-like cells with increased expression of α-smooth muscle actin, vimentin, and collagen (567). Inflammation, chronic hypoxia, BMPR2 mutations, increased flow, and shear stress have all been implicated in EndMT (218, 257, 491, 567). Proliferation of the adventitial fibroblasts as well as EndMT leads to changes in the vascular ECM with increased proteolytic enzymes like matrix metalloproteinases (MMPs), metalloproteases, serine elastases, lysyl oxidases and a decrease in the tissue inhibitors of metalloproteinase (TIMPs). This imbalance results in increased collagen deposition, cross-linking of collagen (conversion of soluble to insoluble collagen), elastin deposition and breakdown, and deposition of fibronectin and tenascin. This change in the ECM milieu results in pulmonary vascular remodeling with increased PVR and decreased compliance (77, 253, 345, 589). Animal models with increased expression of MMPs have exaggerated pulmonary vascular remodeling in response to monocrotaline or chronic hypoxia, and, conversely, rats with overexpression of serine elastase inhibitors have an attenuated increase in PAP and pulmonary vascular remodeling when exposed to hypoxia (201, 651). Rodent models of PH (both monocrotaline and chronic hypoxia) have demonstrated that administration of serine elastase inhibitors decreases elastolytic activity, reduces muscularization of nonmuscular distal pulmonary arteries, and lowers PAPs (128, 265, 589, 643).

Pulmonary vasculature

The changes in the pulmonary vasculature differ based on the etiology of PH. BPD is characterized by an arrest in the lung alveolar and vascular development, leading to decreased capillary density and alveolar-capillary area for gas exchange (79). The neonatal rodent hyperoxia model for BPD has demonstrated that the extent of alveolar simplification

(less complex interstitial structure with decreased alveolar number and septation) and decreased vessel density depends on the concentration of inspired oxygen and occurs in a dose-dependent manner (615). Angiogenesis, the development of sprouts from existing blood vessels, helps in branching of vascular networks in the developing fetal lung, which then coalesce to permit blood flow. Animal model studies have shown that angiogenic signaling is severely impaired in BPD with disrupted vascular endothelial growth factor (VEGF) signaling, decreased pro-angiogenic factors, and increased vasoconstrictor and inflammatory molecules (39, 40). Hyperoxia-induced damage to the pulmonary microvasculature also causes persistent irreversible pulmonary artery medial thickness and increased EC cytoplasm content (431). Impaired angiogenic signaling leading to decreased microvascular cross-sectional area, impaired vasoreactivity, and increased vascular tone together contribute to increased PVR in BPD-PH. Increased PVR and chronic hypoxic vasoconstriction further lead to pulmonary vascular remodeling with intimal hyperplasia and muscularization of small pulmonary arteries (18, 39, 40, 99, 220). This mechanism of impaired angiogenesis due to the arrest in lung development in BPD is different from that seen in IPAH or HPAH, for example, where the pulmonary vasculature and alveolar growth are usually complete before vascular remodeling happens. The pulmonary vascular remodeling in IPAH/HPAH involves intimal and medial hyperplasia of the muscular pulmonary arteries and distal muscularization of the nonmuscular arteries and precapillary arterioles (536). This is accompanied by proliferation and migration of PASMCs, endothelial-to-mesenchymal transition, and the development of vaso-occlusive lesions comprising PAECs, PASMCs, and migratory and inflammatory cells (596). This fixed obstruction seems to be more dominant in IPAH/HPAH, whereas the dynamic obstruction due to altered vasoreactivity and imbalance between vasodilatory and vasorelaxant mediators is more prominent in PH due to chronic hypoxia, even though pulmonary vascular remodeling is a prominent feature in both. Both conditions eventually reduce the pulmonary arterial cross-sectional area, leading to elevated PVR, which aggravates the remodeling process.

Right ventricular changes

Once PVR is elevated, the right ventricle (RV) must pump the blood against increased afterload, thereby causing increased RV strain. This leads to RV hypertrophy over time with increased protein synthesis and cardiac myocyte size without replication. This is at first a compensatory mechanism, but as the RV assumes a more rounded shape, it compresses the left ventricle (LV) and pushes the IVS leftward. The RV hypertrophy leads to progressive contractile dysfunction compounded by the impaired delivery of oxygen and substrates due to the decreased RV vessel density. This, in turn, leads to gradual decompensation with RV becoming dilated, hypokinetic, and fibrotic, causing RV failure (86, 221). Although increased RV afterload is the initiating event for RV failure, a variety of other mechanisms such as neurohormonal signaling, oxidative stress, inflammation, ischemia, and cell death all contribute to right heart failure (86). The key factors leading to RV failure are (i) limited contractile reserve and adaptability to an elevated transpulmonary gradient, (ii) ischemia due to reduced perfusion pressure of the right coronary artery (RCA) from reduced epicardial systolic flow and/or microvascular rarefaction in the RV, (iii) shift from mitochondrial oxidative phosphorylation to cytosolic aerobic glycolysis, and (iv) downregulation and

desensitization of adrenergic receptors in the RV (428, 472, 473, 518). RV failure is the primary cause of death in pediatric and adult PH, and three-dimensional echocardiography of RV function correlates with the severity of pediatric PH (283). In addition to RV systolic failure, PH is also characterized by RV diastolic dysfunction, which is related to RV muscle mass and afterload (196). Decreased RV output leads to impaired LV filling and cardiac output (CO), and decreased LV filling decreases the ability of the LV to assist the failing RV, setting up a feed-forward loop. RV diastolic dysfunction and leftward IVS deviation also impair LV filling and hence diastolic ventricular interaction is as important as systolic interaction in the pathogenesis of heart failure in PH (93, 195).

Molecular Mechanisms

Although many advances have been made in the field of pulmonary vascular biology and molecular mechanisms regulating PVR, much of it is still poorly understood.

NO-sGC-cGMP pathway

NO is synthesized inside endothelial cells by the enzyme endothelial NO synthase (eNOS, NOS3), which cleaves the terminal amino group from the NO precursor, L-arginine, and combines oxygen to generate NO and L-citrulline (461) (see Figure 3). NOS3 gene, which codes for eNOS transcript, is present on chromosome 7. There are two other NO synthases, neuronal and inducible NOS, neither of which are expressed normally in the endothelium. Decreased eNOS expression and function is an important factor in the development of PPHN (251). eNOS uses 5,6,7,8-tetrahydrobiopterin (BH4), nicotinamide adenine dinucleotide phosphate (NADPH), flavin adenine dinucleotide (FAD), and Ca^{2+} as cofactors. BH4 reduces molecular oxygen to form water, a process coupled to the oxidation of L-arginine to generate NO and L-citrulline. Reductions in BH4 lead to uncoupling of NOS and the reduction of oxygen to superoxide anion instead of water. Superoxide can combine with NO to produce peroxynitrite, which is a potent vasoconstrictor (306). NO works in a paracrine fashion and diffuses out of the endothelial cell and into the smooth muscle cell present in the medial layer of the vessel wall. Here it stimulates soluble guanylate cyclase (sGC), which converts GTP into cyclic 3′,5′-guanosine monophosphate (cGMP), which then activates cGMP-dependent protein kinases, namely, protein kinase G (PKG1) (422). NO-cGMP signaling has been established as one of the key pathways in vascular smooth muscle cell relaxation (410, 451). PKGs, which are responsible for most of the intracellular actions of cGMP, are serine/threonine protein kinases with PKG-I being the predominant isoform in the vascular cells (105). PKG decreases intracellular Ca^{2+} concentrations by phosphorylation and inactivation of voltage- and receptor-gated Ca^{2+} channels, which reduce the influx and increase the efflux of Ca^{2+} (232). cGMP also activates myosin light chain phosphatase, which then decreases vascular tone (343). Acute hypoxia has been shown to decrease PKG activity in fetal pulmonary vascular smooth muscle in animal models of PH, hence indicating decreased NO responsiveness (433). Adult studies have shown decreased levels of eNOS expression in the pulmonary endothelium of the lungs of patients with plexiform PH (206). A dysfunctional NO-sGC-cGMP-PKG pathway is one of the key players in disrupted endothelial cell function and pathogenesis of PH. This results from abnormal eNOS expression, reduced NO production due to eNOS uncoupling, diminished

NO bioavailability due to oxidative stress, diminished activities of sGC and PKG, and increased activity of phosphodiesterase-5 (197). Phosphodiesterases (PDEs) are a superfamily of enzymes, from PDE-1 to 11, which can inactivate cAMP and cGMP. The major cGMP-degrading PDE is PDE-5, which is abundantly expressed in the lung tissue. PDE-5 is inhibited by the drugs sildenafil and tadalafil, which are currently used for the treatment of PH (471).

Prostacyclin (PGI2)

PGI2, which is produced by endothelial cells under shear stress, has a variety of functions including inhibition of smooth muscle cell proliferation, vasodilatation, and antiplatelet aggregation. Phospholipase A2 catalyzes the conversion of membrane-bound lipids in endothelial cells to form arachidonic acid (395). Cyclooxygenase-1 (COX2) converts arachidonic acid into intermediate prostaglandins, which serve as precursor molecules to a host of other mediators, including PGI2, which is formed from PGH2 by the action of prostacyclin synthase (PGIS) (396). Both COX-1 and PGIS are abundantly expressed in the endothelium. PGI2 acts via the IP receptor and adenylate cyclase to convert adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP). Increased levels of cAMP mediate increased protein kinase A activity and vascular smooth muscle cell relaxation (Figure 4) (16). Studies in neonatal lambs with PPHN demonstrated that PGIS, COX-1, and COX-2 activity are decreased, contributing to impaired angiogenesis (369).

In the monocrotaline model of rat PH, COX-2 knockout mice showed increased pulmonary oxidative stress and vasoconstriction. Similarly, the hypoxic mouse model for PH showed that hypoxia induced PH and vascular remodeling was exacerbated in COX-2-deficient pulmonary artery smooth muscle cells (186, 534). Adult lung specimens with severe PH showed a complete lack of PGIS expression in the large pulmonary arteries (598).

Endothelin

ET-1 is a potent endogenous vasoconstrictor and also causes vascular smooth muscle cell proliferation. ET-1 is produced by endothelial cells and acts on the neighboring SMCs in a paracrine fashion (640). Hypoxia, ischemia, and shear stress activate the prepro ET-1 gene promoter, which transcribes the preproET-1 peptide, the precursor molecule of ET-1 (191). NO and PGI2 have been shown to inhibit ET-1 release, resulting in pulmonary vasodilatation (480, 492). ET-1 binds to either ET_A receptors found in SMCs and cardiac myocytes or to ET_B receptors located in SMCs and endothelial cells. ET-1 binding to ETA on SMCs activates phospholipase C, which increases intracellular Ca^{2+} concentration through increased inositol triphosphate, leading to vasoconstriction (478). However, activation of endothelial ET_B receptors leads to the release of NO and PGI_2, increased pulmonary clearance of ET-1 and exerts a mild vasodilator effect (121, 248). ET-1 increases ECM proteins and fibronectin production. ET-1 was shown to enhance the effects of transforming growth factor-beta and platelet-derived growth factor, leading to fibrosis, vascular hypertrophy, and smooth muscle cell proliferation (364). Experimental animal models of hypoxic PH have shown increased ET-1 as well as both ET_A and ET_B receptors, and newborn models have shown that ET_A blockade partly reverses the effects of hypoxic pulmonary vasoconstriction (19, 348, 553). ET_A antagonism in a monocrotaline model of

PH decreased the RVH and pulmonary vascular thickening significantly, whereas ET_B antagonism worsened both endpoints, thereby suggesting the divergent roles of ET_A and ET_B in PH (442).

Serotonin (5-HT)

5-HT is a potent pulmonary vasoconstrictor and angiogenic agent synthesized from the amino acid L-tryptophan by tryptophan hydroxylase (TPH) and metabolized by monoamine oxidase (MAO). In patients with PAH, TPH expression in PAEC is increased and 5-HT acts in a paracrine fashion on the PASMCs to induce proliferation and contraction and inhibition of voltage-gated K+ channels causing increased vascular tone (162, 339). Serotonin has also been implicated in the activation of mitogen-activated protein kinases through superoxide production and increasing the susceptibility of BMPR2-deficient mice to developing hypoxia-induced PH (344, 361). PAECs and PASMCs isolated from PPHN lambs show increased levels of 5-HT, which contributes to increased PVR through activation of the 5-HT2A receptor, and selective serotonin reuptake inhibitor (SSRI) infusion also increases PVR in the lamb PPHN model (144, 145). 5HT2A and serotonin transporter expression is also increased in the nitrofen CDH model for pulmonary hypoplasia and PH (255). A recent meta-analysis also found that prenatal exposure to SSRIs or serotonin norepinephrine reuptake inhibitors significantly increased the risk of PPHN after birth (OR 1.82, 95% CI = 1.31–2.54) (378).

Reactive oxygen species (ROS)

Multiple studies have shown that increased oxidative stress is a key contributory factor in the pathogenesis of PH as shown in Figure 5 (129, 148, 181, 267, 620). Oxidant stress can disrupt eNOS function by impairing the eNOS chaperone, heat shock protein 90 (Hsp90), depleting BH4, or its many other cofactors (625). In addition, reactive oxygen species (ROS) causes PASMC proliferation, which is attenuated by antioxidants (619, 621). In energy metabolism, oxygen acts as an electron acceptor in the mitochondrial respiratory chain and gets reduced to water eventually. Electron leak in the respiratory complex chain can lead to formation of several ROS such as superoxide anion ($O_2^{\bullet -}$) and hydrogen peroxide (H_2O_2). Exposure to hyperoxia, uncoupling of eNOS, increased activity of NADPH oxidase, and mitochondrial dysfunction contribute to increased concentrations of ROS (365). Superoxide can combine avidly with endogenous NO to form peroxynitrite ($OONO^{\bullet -}$), which is a potent vasoconstrictor and also reduces endogenous NO activity by nitration of Hsp90 to decrease its association with eNOS (230). eNOS uncoupling, which can happen due to increased $OONO^{\bullet -}$ levels, itself promotes mitochondrial dysfunction and leads to increased levels of $OONO^{\bullet -}$, thus causing a feed-forward pathway (573). Superoxide is converted by superoxide dismutase (SOD) into H_2O_2 under normal conditions, which is further degraded by scavengers such as catalase and glutathione peroxidase. Both superoxide and H_2O_2 also stimulate PDE5, which degrades cGMP, thereby potentiating vasoconstriction (173, 175, 424). H_2O_2 also produces hydroxyl free radicals in the presence of iron through the Fenton reaction, which can cause cell damage. PPHN lambs show increased levels of superoxide and H_2O_2 and NADPH oxidase activity along with decreased sGC activity and impaired angiogenesis (91, 587, 623, 626). PPHN lambs also show decreased levels of mitochondrial DNA copy number and electron transport chain complexes, which thereby lead to

accumulation of ROS. This decrease was shown to be dose dependent in relation to oxygen exposure after birth and partly improved by exposure to NO and by reduction in oxygen concentration (11). Other animal models of PH such as the mouse hyperoxia, piglet hypoxia, and the monocrotaline model have all shown increased levels of NADPH oxidase (74, 148, 181, 608). ROS are removed by scavengers including superoxide dismutase (SOD), catalase, and glutathione peroxidase. Overexpression of extracellular SOD ameliorates PH in rats, protects lung development, and attenuates pulmonary vascular remodeling in hypoxic mice (14, 286, 443, 625). Catalase breaks down H_2O_2, and although mice deficient in catalase develop normally, intratracheal administration of catalase to ventilated PPHN lambs improves oxygenation, increases extracellular SOD activity, decreases superoxide levels, decreases PDE5 activity, and increases cGMP levels in the pulmonary arteries (176, 623).

Potassium (K) channels

Reduced K^+ channel expression and activity contribute to depolarization of SMCs in hypoxic PH, and increasing K^+ channel expression in PASMCs attenuates changes of PH (96, 647). Oxidative stress has been found to impair the vasodilatory voltage-gated Kv channels in PPHN models, which can be partly restored by superoxide scavengers (313). Depolarization is believed to mediate the increased Ca^{2+} influx via voltage-gated Ca^{2+} channels (VGCCs) (537). Administration of dichloroacetate, which inhibits glycolysis, increases the expression of K+ channels and attenuates pulmonary vascular remodeling in both hypoxic and MCT models of rat PH (383, 389).

Calcium (Ca) channels

Increased cytosolic Ca^{2+} is a major trigger for pulmonary vasoconstriction and PASMC proliferation and migration, leading to remodeling. Increased resting cytosolic levels of Ca^{2+} as well as increased Ca^{2+} influx have been noted in PASMCs isolated from PH models. Both VGCCs and TRPC ion channels have been implicated in the Ca^{2+}-mediated pulmonary vascular remodeling and PH pathogenesis. Voltage-gated channels, which are of L and T types, open in response to membrane depolarization and result in Ca^{2+} influx. Hypoxic mice that developed PH have increased expression of both L-type and T-type Ca^{2+} channels on vascular SMCs (614). Chronic hypoxia has been shown to upregulate L-type Ca^{2+} channels in small pulmonary arteries of the neonatal models of PH, and the calcium channel blocker, nifedipine decreased pulmonary pressures in the same model by inhibiting voltage-gated Ca^{2+} influx (249). Similarly, Rodman et al found an abundance of T-type Ca^{2+} channels in the medial layer of pulmonary arteries, and siRNA-induced inhibition of these channels decreased PASMC proliferation *in vitro* (501). TRPCs, which are Ca^{2+}-permeable nonselective cation channels, have been implicated in IPAH and are increasingly recognized as the primary contributors for a sustained increase in cytosolic Ca^{2+}. These, unlike VGCCs, are modulated by phosphorylation, receptor activation, or store depletion. PASMCs from patients with IPAH have increased expression of TRPC3 and TRPC6, and similar increased expression has been found in hypoxic PH models (357, 617). Decreasing the activity of TRPC6 either pharmacologically or by RNA silencing decreased the expression of the TRPCs as well as decreased vascular tone in the pulmonary arteries (321, 357). Data about Ca^{2+} and PAECs are still conflicting as *in vivo* models have failed to show elevated

intracellular Ca^{2+} levels in PAEC isolated from hypoxic rats. However, cultured PAECs from these rats show increased Ca^{2+} levels and increased expression of TRPC4 (170, 459).

Vascular endothelial growth factor (VEGF)

Several different vascular endothelial growth factor (VEGF) splice variants have been identified, of which VEGFA is the most prominent and known for its functions of vascular permeability, angiogenesis, and vascular cell survival (307). VEGFA binds to two different receptor tyrosine kinases (RTKs), VEGFR1 or fms-related tyrosine kinase-1 (Flt1) and VEGFR2 or fetal liver kinase-1 (Flk1). VEGFR1 acts as a negative regulator of VEGF by preventing activation of VEGFR2, which is the functional receptor mediating the mitogenic, proangiogenic, and permeability-enhancing actions of VEGF (307, 463). Most animal studies, including both hypoxic and monocrotaline PH models, have shown increased VEGFA, VEGFR1, and VEGFR2 levels, which have been linked to increased endothelial cell proliferation in PH (118, 119, 599). In contrast, fetal lamb models of *in utero* generated PH have shown decreased VEGFA levels in endothelial cells, and VEGFA administration improved angiogenesis *in vitro* (208, 586). These studies highlight the developmental origin of fetal and neonatal PH. The causal relationship of VEGFA in pulmonary arterial remodeling needs further study. However, administration of VEGFA ameliorates the changes of PH in hypoxic animal models, which suggests that the relationship between VEGF, VEGFRs, and PH is complex and context dependent (172, 464). VEGFR inhibition causes apoptotic and emphysematous changes in rat lungs, but when exposed to chronic hypoxia, these rats develop pulmonary vascular angio-proliferative changes leading to severe PH (290, 341, 583). Cord blood levels of VEGFA are decreased in babies with maternal placental hypoperfusion and coexisting BPD-PH, thereby indicating that disrupted angiogenesis starts *in utero* and contributes to BPD-PH pathogenesis (387). Autopsy specimens have shown increased VEGF and VEGFR1 levels in both BPD-PH and PPHN, likely as a compensatory effect of disrupted endothelial function (332).

Other growth factors

Apart from VEGF, several other growth factors contribute to the pathogenesis of PH. Adult patients with PAH have shown increased expression of basic fibroblast growth factor (bFGF) in plasma and urine (66). Animal models of pediatric PH have shown elevated levels of FGF2 in PASMCs and PAECs (622). FGF-2 has also been shown to be an inducer of VEGF expression *in vitro* via its primary receptor FGFR-1, both of which are upregulated in PH (533). FGFR-1 knockout mice, when exposed to hypoxia, developed significantly less right ventricular remodeling and had lower RV systolic pressures, and pharmacological inhibition of FGFR-1 using SU5402 nearly reversed a rat model of PH (275). Current knowledge indicates that FGF-2 modulates pulmonary vascular remodeling and PH through the FGFR-1. Hepatocyte growth factor (HGF) levels have been shown to be decreased in hypoxic conditions and in the monocrotaline model (242, 453). HGF gene transfer has also been shown to ameliorate changes of MCT-PH (452).

Platelet-derived growth factor (PDGF) is a mitogen that contributes to vascular remodeling through smooth muscle hyperplasia in chronic PH. PDGF mostly consists of two polypeptide chains, A and B, although later studies have found that C and D chains exist as

well. These chains can form dimer isoforms (AA, BB, CC, DD, and AB) and are structurally and functionally analogous to other growth factors like VEGF. They act on two primary tyrosine kinase receptors, PDGF receptor α (PDGFR-α) and PDGF receptor β (PDGFR-β) (24, 187). PDGF-A binds to PDGFR-α, whereas PDGF-B can bind to both receptors. PDGF-A and C are expressed in epithelial cells, whereas PDGF-B is expressed in megakaryocytes and endothelial cells, and PDGF-C and D are expressed in fibroblasts and in vascular SMCs, respectively (22, 24). PDGFR-α is expressed on mesenchymal precursor cells in the lungs, whereas PDGFR-β is expressed in SMCs. Hypoxia is the most common trigger of the PDGF/PDGFR-β pathway leading to a switch in the phenotype of SMCs from the contractile to proliferative phenotype (24, 585, 655). Studies in the ductal ligation lamb model of neonatal PPHN have shown that selective inhibition of PDGF-B decreases RV hypertrophy and pulmonary arterial thickening and increases PDGFR-α and β expression (41). Monocrotaline-induced PH models have shown increased levels of PDGF-B early in the disease process, which decreased to below control levels as the disease progressed (27). Lung specimens from patients undergoing transplants for IPAH have shown increased levels of both PDGF-A and B, as well as PDGFR-α and β in the PASMCs (468). More recently, microRNA-30c, which inhibits PDGFR-β translation, has been implicated in hypoxic PH. Hypoxia leads to decreased levels of microRNA-30c, which causes PDGFR-β overexpression, leading to a switch from the contractile to synthetic type SMCs (637). Both hypoxic and monocrotaline models of PH showed increased expression of PDGF-B and PDGFR-β; inhibition of PDGFR-β has reversed PH in these models (526).

Transforming growth factor (TGF)-β superfamily includes several cytokine growth factors, which play a critical role in regulation of cell growth and differentiation. Bone morphogenetic protein receptor type 2 (BMPR2), ALK1, endoglin, and caveolin-1 are membrane-bound receptors of the TGF-β superfamily, which have been implicated in pediatric PH (188, 238, 648). Caveolin-1 has a cell-specific role in PAH with loss of Cav1 from PAEC and high Cav1 levels in SMC being associated with vascular remodeling, including higher fibroblast proliferation, aberrant Ca^{2+}, and high levels of oxidative stress (377). *ALK1* mutation has been associated with younger age at diagnosis and death compared to patients with no mutations and a female predominance, with a female-to-male ratio of 3.5 (211).

Hypoxia inducible factors (HIFs)

HIF-1 and 2 are important transcriptional regulators of the physiological response to hypoxia. HIF-1 has two subunits, α and β, and is a highly conserved transcription factor that regulates the oxygen-dependent expression of hundreds of genes. The β subunit is constitutively expressed, whereas the α subunit only accumulates under hypoxic conditions due to decreased hydroxylation and stabilization from decreased proteasomal degradation (479). HIF-1α then dimerizes with HIF-1β, translocating to the nucleus and activating several genes. Mice heterozygous for HIF1-α null allele when exposed to chronic hypoxia showed significantly less RVH, less RV pressures, and decreased medial thickness compared to wild-type mice (646). At the same time, the heterozygous knockout mice showed an attenuated increase in TRPC expression, cytosolic Ca^{2+}, and Na^{+}/H^{+} exchanger-isoform 1 and did not show reduced expression of plasma membrane K^{+} channels in response to

chronic hypoxia, demonstrating a protective effect from PH. The HIF-1α downstream targets, which have been implicated in PH, are ET-1, VEGF, and HEK-2. Hypoxia upregulates ET-1 as well as HIF-1α expression in the lungs, and both ET-1 and HIF-1α upregulate each other's expression, thereby creating a feed-forward loop (350). This effect of ET-1 on HIF-1 expression is only seen in PASMCs and not in aortic SMCs. The fetal ductal ligation lamb model where decreased angiogenesis contributes to the development of PPHN has shown increased HIF-1 expression in PASMCs, and inhibiting HIF-1 expression increased VEGF expression and improved angiogenesis in the PPHN lambs (373, 624). HIF-2 has been shown to activate EPO gene expression, which increases erythropoietin production. Endothelial-specific HIF-2 knockout abolishes PH and right ventricular responses to chronic hypoxia (260).

Rho proteins

RhoA is a member of the Rho family of small GTPases and regulates a variety of cellular responses such as cell contraction, migration, growth, gene expression, and differentiation (164). Activation of RhoA occurs via stimulation of G-protein-coupled receptors by receptor and non-receptor tyrosine kinases; inactivation can occur via protein kinase G, which is activated by the NO-sGC-cGMP pathway. There is also evidence that hypoxia leads to RhoA activation in PAECs and PASMCs (581). RhoA activates its downstream target Rho-kinase (ROCK), which has been widely implicated in PH. In models of neonatal and adult PH, high ROCK levels cause elevated vascular tone, increased myogenic reactivity, and pulmonary vascular remodeling (209, 382, 429, 447). ROCK primarily phosphorylates the myosin-binding subunit of myosin light chain phosphatase (MYPT-1), and thereby increases phosphorylation of myosin light chain and enhances the contraction at any given level of activity of myosin light chain kinase (MLCK) and cytosolic Ca^{2+} (168, 554). In addition to vascular smooth muscle cell contraction, ROCK affects endogenous NO action by reducing eNOS mRNA stability (335). ET-1, which is a potent vasoconstrictor, has been shown to activate ROCK to cause impaired angiogenesis in fetal lamb PPHN PAECs *in vitro* (209). ROCK inhibitors, Y-27632 and fasudil, have been shown to inhibit pulmonary artery myogenic responses in hypoxia-exposed adult rats and fetal sheep and to reverse sustained vasoconstriction in response to chronic hypoxia or ET-1 infusion (94, 168, 384, 594, 628). ROCK inhibitors, when systemically administered at the onset of injury in the chronic hypoxia or monocrotaline PH model, prevent changes of PH (1, 168).

Bone morphogenetic protein receptor type 2 (BMPR2)

Mutations of the BMPR2 gene, present on 2q33, have been identified in IPAH and HPAH, and children with BMPR2 mutations are less likely to respond to acute vasodilator testing (13% vs 44%) and are more likely to have severe disease at diagnosis (32, 147, 508). More than 140 distinct BMPR2 mutations have been found and together they are present in 10% to 40% of families with PAH (631). A French cohort found 5 different BMPR2 mutations in children with IPAH/HPAH, along with other mutations in ACVRL1 and TBX4 (347). Presence of a BMPR2 mutation does not guarantee development of the clinical features of PAH, which suggests that there is decreased penetrance. The mechanisms and factors that lead to PAH in some individuals with BMPR2 mutations remain unclear; Figure 6 shows the pathways disrupted in BMPR2 mutations that might lead to PAH. The mechanistic role of

BMPR2 mutations in the pathophysiology of PAH is still not clear with most studies indicating upregulation of mitogen-activated protein kinase or reduced activation of transcription factor Smad 1 (515, 642). Several *in vitro* and *in vivo* studies have shown that BMPR2 mutations decrease endothelial cell viability and lead to PASMC proliferation, key features of PAH. Several biochemical alterations have been described in cells with decreased BMPR2 function, including decreased mitochondrial function, increased glycolysis, and excess proliferation of PASMCs. Downregulation of BMPR2 has been reported to contribute to pathophysiology of PAH in patients without specific mutations in this gene. BMPR2 has emerged as a major signaling pathway that is altered in a variety of PAH cases, and therapies to promote this signaling are actively being studied as the next frontier in PAH-specific therapies (485, 634).

Other genes that have been implicated in PAH include ALK1, endoglin, CAV1, and KCNK3, which are associated with autosomal dominant diseases, and EIF2AK4, which is associated with the autosomal recessive form of pulmonary veno-occlusive disease (35).

Notch pathway

Notch pathway is a highly conserved canonical pathway important for the determination of cell fate during embryonic development. It consists of the four mammalian Notch receptors —Notch 1 to 4—and five ligands—Delta-like (Dll) 1, 3, 4 and Jagged (Jag) 1 and 2 (392). The interaction of the ligand with the membrane-bound Notch receptor leads to its proteolytic cleavage to release the Notch intracellular domain (NICD), which translocates to the nucleus to activate the C-promoter binding factor 1 (CBF-1). CBF-1 binds to the NICD to form an active transcription factor complex to target the downstream genes belonging to HEY/HES family (318, 638). Notch 1, 3, and 4 and Dll-4, Jag-1 and Jag-2 are present in the human arterial system and are critical to maintaining normal vascular structure, angiogenesis, and vascular remodeling (224, 256, 369). Both hypoxic and MCT models of PH have shown increased expression of Notch 3 and the Notch 3 intracellular domain, and Notch knockout mice do not develop hypoxic PH (352). Chronic hypoxia increases the expression of store-operated Ca^{2+} channels (SOCE) and activates Notch signaling, and blockade of the TRPC6, a key canonical SOCE, inhibits acute hypoxic pulmonary vasoconstriction and development of PH in chronic hypoxia (552). Notch 3 and its target HES-5 are expressed highly in PASMCs of patients with PAH, and knockdown of HES-5 attenuates the vascular proliferative effects produced by increased expression of Notch 3 *in vitro* (352). Notch 3 inhibition by itself in hypoxic neonatal rat pups also prevents the changes of chronic PH and decreases PDGFR-β content in the PASMCs (269).

Peroxisome proliferator-activated receptor (PPAR)

PPAR is a member of the nuclear receptor hormone superfamily and is widely expressed in PAECs and PASMCs, where it regulates vascular SMC proliferation (578, 653). Animal models of PPHN have shown decreased levels of PPARγ with increased levels of SOCEs like TRPC1 and TRPC6 (159). PPARγ seems to have a protective effect against PH, as evidenced by the development of spontaneous PH in mice with selective deletion of PPARγ in PASMCs (234). PPAR-γ deletion *in vitro* also induces PASMC proliferation in cultured human cells, whereas overexpression reduces the same (80). In PPARγ-deficient pulmonary

microvascular endothelial cells, migration and angiogenic ability were significantly attenuated via E2F1-mediated gene regulation (607). MCT rat models of PH treated with PPARγ agonists, pioglitazone or troglitazone, were protected against pulmonary vascular remodeling (379, 636). In rats exposed to hypoxia for 3 weeks, rosiglitazone (a PPARγ agonist) attenuated hypoxia-induced RVH, vascular SMC proliferation, pulmonary vascular collagen and elastin deposition, and matrix metalloproteinase activity. Rosiglitazone, however, failed to attenuate hypoxia-induced increases in PAP, which was attributed to the inability of PPARγ ligands to modulate ROCK signaling, a critical mediator of pulmonary vasoconstriction (131, 223). PPARγ ligands decrease hypoxic Nox4 expression, oxidative stress, and PDGF signaling in the lung (441). PPARγ activation also decreases the levels of ET-1 and asymmetric dimethylarginine (an endogenous NO synthase inhibitor), both of which are involved in the pathogenesis of PH (289, 500).

MicroRNA

MicroRNAs (miRs) are short approximately 22 base pair long nucleotide sequences that are conserved across species and produced from transcription of noncoding DNA. miRs can bind to the 3’ untranslated region of mRNA and repress the translational mechanism and hence can modulate several disease processes. Each miR can bind to multiple mRNAs based on the degree of the complementarity between their sequences, and each mRNA has binding sites for multiple miRs. This leads to a complex interplay; hence several miRs have been implicated in PH disease processes. miR-21 is downregulated in the MCT model of rat PH and in human lung tissue and serum of patients with PAH (104). However, hypoxic PH models have shown contrasting results; miR-21 levels were elevated in distal small arteries and downregulating miR-21 expression both *in vivo* and *in vitro* decreased PASMC proliferation and pulmonary vascular remodeling (641). miR-21 has several targets, including BMPR2 and dimethylarginine dimethyl-aminohydrolase 1 (DDAH-1), which decreased with increasing levels of miR-21 (264, 484, 641). DDAH-1 is responsible for the metabolism of asymmetric dimethylarginine, which is an endogenous NOS inhibitor. PPAR-γ, which attenuates the effects of hypoxic PH, also decreases miR-21 expression in the presence of hypoxia (222). These data indicate that miR-21 is a likely contributor to pulmonary vascular remodeling due to hypoxia and is therefore a potential therapeutic target for PH. Other miRs like the miR 17 to 92 cluster, miR-145 and miR-210 are also upregulated in experimental models and contribute to PASMC migration and proliferation and PAEC proliferation and resistance to apoptosis. miR-124 has been found to be downregulated in PH and contributes to fibroblast migration, proliferation, and activation in addition to effects on PASMCs (657).

Animal Models of PH

There are multiple preclinical animal models of PH, based on the different pathological states resulting in the final syndrome of elevated PAPs. Understanding the animal models is essential to understand the different molecular mechanisms and treatment strategies targeting PH.

Rat and mouse models have been used to study PH extensively, the most common models being the chronic hypoxia (CH) and the monocrotaline (MCT) models. These models have different strengths and limitations. In general, rat models show more robust vascular remodeling and RVH compared to mouse models and are more widely used for the investigation of PAH pathogenesis. In contrast, mouse models offer a wide array of genetic knockouts and transgenic overexpression to investigate the role of specific signaling pathways *in vivo*. However, mouse models of hypoxia or monocrotaline fail to develop the full spectrum of vascular remodeling observed in human PH. One of the most commonly used rat models for PAH involves the injection of monocrotaline. Monocrotaline, which is a plant-based alkaloid, is activated *in vivo* by cytochrome P-450 enzymes to form monocrotaline pyrrole (MCTP), which causes endothelial injury (388). This leads to a cascade of pulmonary vasculitis, PAEC apoptosis, PASMC proliferation, and pulmonary vascular remodeling, leading to obstructive vasculopathy in the pulmonary vasculature. The TGFβ-Smad-BMPR2 signaling pathway is one of the key pathways implicated in the MCT model, along with inflammation and cytokine release playing contributory roles (366). Downregulation of BMPR signaling has been reported in this model in several studies. The MCT model has been criticized as experimental treatments targeting different pathways have shown striking improvements with almost a complete reversal of the PH changes. The rapid response to therapeutic agents with a reversal of PAH changes, which are not found in PAH patients, raised concerns that this model is not reflective of human disease and that the endpoints do not correlate with progression of PH in patients. Chronic hypoxia (CH) model for PH is closely representative of Group 3 PH; however, it has been used for neonatal PPHN studies as well (293). Once altitude and low oxygen tension were found to be causally involved in heart failure in cattle living at >8000 feet in Colorado, several animal CH models have emerged. Animals in these studies are placed in hypobaric or normobaric hypoxia, which induce chronic oxygen deprivation, hypoxic pulmonary vasoconstriction, and pulmonary vascular remodeling. The effects of hypoxia are varied across different species, but most models show extensive vascular remodeling. Rats exhibit consistent increases in mean PAPs, right ventricular mass as well as PASMC hypertrophy and hyperplasia and distal muscularization (486, 568). Mouse CH models, although useful for widely available genetic knockouts, have failed to demonstrate similar changes in PASMC. Mice consistently show less vascular remodeling compared to hypoxic rats or humans, which have less remodeling compared to neonatal calves (60, 458, 568). This might be attributed to differing genetic responses between the two species; CH rats show increased expression of genes involved in EC proliferation and decreased expression of pro-apoptotic genes, whereas CH mice demonstrate decreased expression of genes involved in vascular SMC proliferation (95). Hypoxia-induced inflammatory response also plays a role in the development of PH as evidenced by the presence of early and persistent inflammatory infiltrates (primarily mononuclear cells) along with adhesion molecules and cytokines within the vessel wall (97, 568). One of the prominent issues with the rat CH model is that although pulmonary pressures and RV size are increased, RV failure does not usually occur. Of special note are fawn-hooded rats, which have an inherited deficiency in platelet serotonin uptake, and they develop PH ~4 weeks of life, and this is accentuated by exposure to hypoxia. They also demonstrate decreased alveolarization, lung hypoplasia, and immaturity, which make them suitable for studying BPD-PH (340). Hypoxic vasoconstriction is attenuated in newborns,

likely due to enhanced PGI2 release; hence the CH model is not ideal for studying PPHN or neonatal PH.

The combination of Sugen 5416 (SU5416), a VEGF receptor inhibitor and hypoxia, leads to the development of angio-obliterative lesions in rat lungs causing profound PH, more so than hypoxia alone. In mice, it has similar effects with the evolution of a severe PH phenotype compared to hypoxia alone, but it does not produce the same effects of angio-obliterative lesions (610). There have been some critiques of the model related to its almost irreversible and unresponsive PH phenotype, but proponents of the model argue that it more closely resembles the severe type of human PH.

Unique for neonatal and pediatric populations is PH associated with BPD. The alveolar and vascular simplification observed in these infants has been linked to and reproduced by neonatal exposure to hyperoxia. Mice exposed to hyperoxia from postnatal day 1 to 4 showed decreased lung elastance, RVH, reduced distal microvasculature, and reduced expression of BMP receptors and downstream phospho-Smad-1/5/8 (644). Hyperoxia exposure has been shown to increase PDE5 expression in PASMCs and decrease cGMP signaling leading to PH and RVH, which are partly reversed by PDE5 inhibitor, sildenafil (173, 244, 342). Short-term exposure to hyperoxia has been shown to induce mitochondrial matrix ROS, which activate PDE5 in a cGMP-dependent protein kinase-dependent manner in the PASMCs (175). Riociguat, which stimulates sGC, responsible for production of cGMP from GTP, has been shown to prevent lung injury, decrease RV systolic pressure, RVH, and distal pulmonary arteriolar muscularization in hyperoxic neonatal mice (154). Mice with mutations in BMPR2, which itself can lead to PH, when exposed to hyperoxia demonstrated a significantly worse PAH phenotype with increased RV systolic pressure, increased pulmonary vascular occlusion, and decreased cardiac output (179).

PPHN, a unique disorder in which newborns have elevated PAPs at birth, is most closely reproduced by the fetal lamb ductal ligation model (314). The ductus arteriosus, which diverts the blood away from the lung *in utero*, is mechanically constricted in the fetus to elevate the PVR. Although the pulmonary blood flow increases as well initially, within 2 h it comes back to the baseline, whereas the PVR remains elevated. Fetuses usually survive to delivery and the newborn demonstrates clinical signs of PPHN with elevated PAPs and hypoxemia and morphologic changes of pulmonary vascular remodeling, fibrosis and muscularization of nonmuscular arteries (565). PPHN lambs have been shown to express decreased eNOS gene expression with increased production of ROS from uncoupled eNOS, which contributes to the PPHN phenotype (314, 535). Administration of glucocorticoids and ROS scavengers such as superoxide dismutase attenuate this adaptive response to ROS and restores eNOS function (108, 174). The ductal ligation model shows a clear dose-response relationship of pulmonary vasodilation to NO and was widely used for the preclinical studies, which led to the FDA approval of iNO in PPHN. There have been attempts to create other models of *in utero* PPHN, either by maternal hypobaric hypoxia or by chronic repeated placental embolization. The first model produced growth retardation but not structural or functional changes in the pulmonary vasculature, and the second was associated with high fetal mortality (565).

Models for CDH: PH is a common feature of CDH and is due to prenatal pulmonary vascular hypoplasia and vascular remodeling. The pulmonary hypoplasia is due to the presence of herniated abdominal contents in the thoracic cavity, limiting lung growth *in utero*. The models that have been used so far to study CDH are the surgical models to create diaphragmatic defects in rabbit and sheep, the nitrofen exposure model in rats and mice, and the knockout model in mice. The surgical model is based on a surgical intervention creating a diaphragmatic defect in the fetus, which leads to herniation of intra-abdominal contents into the thorax, leading to impaired lung growth (446). Surgical CDH created in late gestation rabbit fetuses showed an increased medial thickness and a decreased internal diameter of the pulmonary arteries. Creation of *in utero* fetal tracheal occlusion reverses these changes to a certain extent (510, 511). The sheep surgical model has also shown a decreased number of highly proliferative PAECs, and this was hypothesized to be a contributor to the development of pulmonary hypoplasia and impaired angiogenesis, leading to postnatal PH (9). Although this model is valuable for studying *in utero* interventions for fetal repair of CDH like tracheal occlusion or *in utero* repair of defects in the diaphragm, the surgical defect is created relatively late in gestation. Creation of this defect late in gestation may miss certain stages of lung development, which are more affected in the human disease (603). This is also a single-hit lung hypoplasia model, whereas CDH is presumed to be a dual-hit model (292). One of the widely studied models is the nitrofen CDH model. Nitrofen when given by gastric lavage to pregnant rats just before fetal lung and diaphragm development begins induces CDH in 70% of the fetuses and pulmonary hypoplasia in 100% (603). Nitrofen model has led to a better understanding of the two-hit hypothesis of CDH, where nitrofen leads to early bilateral lung hypoplasia before the diaphragm is supposed to close (1st hit) and ipsilateral lung hypoplasia and PH from later herniation of bowel and abdominal viscera into the lung cavity from the diaphragmatic defect (2nd hit) (406, 603). The primary mechanism is believed to be via the retinoid signaling pathway as nitrofen is a retinal dehydrogenase 2 inhibitor, and serum levels of both retinol and retinol binding protein were 50% lower in infants with CDH (229). Various other pathways including VEGF, BMP, and Wnt pathways are also implicated in the dysregulated pulmonary endothelium, PAEC dysfunction, and impaired cross talk between PAECs and PASMCs in nitrofen-CDH. Nitrofen-CDH rats also have increased proliferation and resistance to apoptosis in PASMCs as well as increased secretion of ECM proteins and medial wall thickness of the pulmonary vasculature (404). The pulmonary arterioles show blunted oxygen-induced vasodilatation, which further contributes to decreased vasoreactivity and postnatal PH (125). Several genetic models including knockout models of genes like Wilms Tumor 1 (Wt1), Sonic Hedgehog (Shh), Slit 3, Fog 2, COUP-TFII, Gata 4, and Gata 6 have also been proposed, but a well-defined knockout model is still lacking. Knockouts of retinoic acid receptor genes have resulted in CDH, which is aligned with the altered vitamin A and retinoid signaling pathway hypothesis of CDH (117).

CHD and shunt lesions leading to PHVD is an unique entity that has been studied in lamb and piglet models. The lamb model is created by insertion of a polytetrafluoroethylene graft between the ascending aorta and the pulmonary artery in late gestation, which leads to the elevated pulmonary-systemic blood flow ratio and mPAP, although the PVR is not significantly increased. The model closely simulates infants with left-to-right shunts with

relatively normal Qp/Qs at birth but a progressive increase in Qp during first six weeks of life as the PVR declines postnatally. These lambs develop increased pulmonary vasoconstrictor response to hypoxia and thromboxane A2 (497). One piglet model of CHD-PAH involves shunts between the left pulmonary artery and the subclavian artery, leading to flow-induced PAH and vascular remodeling. These piglets with shunts develop RV failure even with mild PAH, likely due to the decreased levels of VEGF and increased pro-inflammatory cytokines such as interleukin-1a and TNF-β seen in this model (502, 503). Pigs with chronic systemic-to-pulmonary shunting also have increased expression of the pulmonary ET-1 system, which is prevented by the ET receptor antagonists bosentan and sitaxsentan (502, 504).

Diagnostic Evaluation

Pediatric PH has multiple etiologies and a wide spectrum in presentation. Hence, a comprehensive, systematic approach to the diagnosis will aid in the correct classification and choice of treatment. Recent studies have shown that most children do not undergo the full evaluation necessary for an accurate diagnosis of PH (61, 270). Several diagnostic algorithms have been suggested and were modified over the years with more available evidence about the full spectrum of pediatric PH and with changing classifications. The most recent algorithm from the Pediatric Task Force of the 6th WSPH in 2018 is shown in Figure 7. Based on history, biomarkers, echocardiographic, cardiac catheterization, and MRI findings, children with PAH can be stratified into high-risk or low-risk categories (Table 7), which determines treatment arms. Table 8 discusses the recommendations for use of different diagnostic tools in the pediatric PHD.

Chest X-ray

PAH is clinically silent in early stages and not visible on X-ray imaging. Chest X-rays may show features of RA and RV enlargement in later stages. Dilation of central pulmonary arteries and diminished peripheral lung vasculature based on decreased distal pulmonary blood flow may also become apparent with disease progression. Increasing PVR is represented as worsening oligemia in lung fields, particularly in specific disorders, such as primary PPHN. Increasing pulmonary edema or signs of pulmonary venous congestion on X-ray should raise concern for other etiologies like PVS or left ventricular dysfunction leading to back pressure. In specific syndromes such as PPHN or BPD-PH, X-rays may be useful to track the parenchymal lung disease. PPHN due to meconium aspiration syndrome shows hyperexpanded lung fields mixed with scattered areas of atelectasis due to the obstructive nature of meconium in air passages (430). BPD will show signs of chronic lung disease such as increased lung texture and hypolucency (92, 351).

Electrocardiogram (ECG)

ECG changes in pediatric pulmonary hypertension include right atrial enlargement, right axis deviation (RAD), and RVH with secondary T-wave changes (507). A study of electrocardiogram-echocardiogram pairs for known cases of pediatric PH showed a 69% sensitivity and 67% positive predictive value of ECG in predicting PH when echocardiogram was used as the diagnostic gold standard (481). When ECG was compared to cardiac

catheterization for known pediatric PH, the sensitivity, specificity, positive and negative predictive values of RAD and RVH on baseline ECG for disease progression were 92%, 48%, 33%, and 95%, respectively (334). ECG-based screening when applied to a school-based population of children in Japan helped in early recognition and treatment of pediatric PH patients, associated with severe PH and preserved right heart function (525).

Echocardiography

Conventional 2-D transthoracic echocardiography remains one of the most widely used tools to diagnose pediatric PH. The advantages of echo are its noninvasive nature, wide availability, safety and feasibility in the pediatric population. A meta-analysis in adult PH found a pooled sensitivity of 74% and a pooled specificity of 85% in diagnosing PH for echo (437). PH leads to poor right ventricular compliance and RV diastolic dysfunction, leading to progressive right atrial dilatation. Imaging of the RA in the apical four-chamber view to measure the RA major and minor axes and planimetry of the RA area in end-systole will determine the presence of RA dilatation (282). Progression of PH might also lead to inferior vena cava (IVC) dilatation, and estimating the IVC diameter and the presence of inspiratory collapse can help in indirect estimation of the RA pressures. The usual RV:LV area ratio is less than 0.6, and both acute and chronic increases in PA pressures affect this number. Acute PH leading to RV distension and chronic PH leading to ventricular remodeling to maintain cardiac output will increase the RV:LV area ratio assessed by echocardiography.

Estimation of pulmonary arterial pressure (PAP)

The peak tricuspid regurgitation (TR) gradient is the most commonly used estimator of RV systolic pressures, which reflects the systolic PA pressure (sPAP), provided there is no obstruction of blood flow between the RV and PA. The TR gradient is measured as the continuous wave (CW) Doppler velocity across the tricuspid valve in line with the regurgitation flow and is then converted into a pressure gradient using the modified Bernoulli equation [4×(TR velocity)] (276). This is the pressure gradient across the tricuspid valve and hence is the difference between systolic pressures of RA and RV. Adding the RA pressure (usually 5-10 mmHg in pediatric patients) to this number will give the RV systolic pressure, which gives us the estimate of the sPAP. This is not always practical as the TR jet is not present in all patients (418). In the cases of RV outflow tract obstruction, PA stenosis, or ventricular septal defects, the accuracy of estimation of sPAP based on TR jet diminishes (310). Using CW Doppler to measure pulmonary regurgitation (PR), the mean PAP and the diastolic PAP can also be estimated from the early-diastolic and end-diastolic PR velocities, respectively, and then applying the modified Bernoulli's equation. The mPAP can also be calculated from the sPAP as mPAP = 0.61 × sPAP + 2 mmHg (308). Other measures of RV and PA systolic pressures are the measurement of pressure gradient in the presence of a VSD or a PDA and subtracting this from the systemic pressures at that time. PA acceleration time (PAAT), which is the interval in milliseconds from the onset of ejection to the peak flow velocity, is another measure of PVR and a PAAT < 120 ms in children is indicative of PH (107). PVR can also be estimated in children from the echocardiographic estimation by a simple ratio of peak TR velocity to the velocity time integral of the right ventricular outflow tract (VTI-RVOT), with a value of >38 providing a 100% specificity for a PVR of >8 WU

(462, 611). Echocardiographic estimates of PVR are not always accurate, especially when the PVR is very high, and in such situations cardiac catheterization is the next preferred step.

Estimation of RV function

Assessing the RV longitudinal systolic function is an important part of the echocardiographic PH diagnosis, as this RV dysfunction places the patient at a higher risk of complications and mortality and thus potentially changing management strategies. The tricuspid annular plane systolic excursion (TAPSE) is the longitudinal excursion of the tricuspid annulus toward the apex as measured by M-mode, and varies based on gestational age and postnatal age, and there are studies establishing reference values for the same (311, 322). TAPSE is a surrogate for RV function and a decreased TAPSE implies diminished RV function, with a strong correlation (R = 0.86) to RV function estimated by cardiac MRI, considered to be the gold standard (322, 524). The TR jet/TAPSE has also been found to correlate positively and strongly with the NYHA FC, thus implying future use in PH diagnosis and prognostication (309). TAPSE, however, does not document radial systolic RV function, which contributes to the RV ejection in the setting of RV hypertrophy.

RV strain and strain rate are also important measures of RV function, which determine regional wall motion abnormalities, which can be abnormal in PH. Strain is the measure of the myocardial length change from the baseline and strain rate is the velocity of this change (324). The severity of PH in adult patients has a strong correlation with the decreased peak systolic strain, which decreases with increasing RV afterload, and serial measurements of RV systolic strain have been found to be useful in predicting long-term prognosis in adult patients (237, 353). This has not been well studied in pediatric PH, although one study found RV strain to be an early predictor of RV dysfunction in children with IPAH (448). Recently, the RV-arterial coupling ratio using stroke volume to end-systolic volume has been found to be an independent predictor of adverse clinical outcomes in pediatric PH (284). Both TAPSE and RV global longitudinal peak strains have been found to be associated with progression to death or extracorporeal membrane oxygenation (ECMO) in infants with PPHN (374).

Estimation of LV function

Identifying whether there is any left heart disease is important as this can change the management approach of PH completely. LV dysfunction leads to increased LV filling pressures, which in turn can lead to increased back pressure in the pulmonary vascular bed. LV systolic function is measured by the shortening fraction and ejection fraction (EF), with a normal EF being 56% to 78% (254). LV diastolic function is measured by assessing the mitral inflow by Doppler, with biphasic waves that peak during early diastolic filling (E waves) and atrial contraction (A waves). E waves are greater in velocity than A waves, and a reversed relationship between these two implies impaired ventricular filling as a result of decreased relaxation (305). A recent consensus statement from the PPHNet mentioned the importance of measuring LV systolic and diastolic function in babies with BPD-PH as this contributes to worsening pulmonary edema in these patients and needs a different approach (320). A recent study also found some degree of LV diastolic dysfunction through echocardiographic indices in nearly all pediatric patients with PH, thus further stressing the point of assessing LV function during PH diagnosis and evaluation (98). Infants with PPHN

who have diminished LV size and function have increased mortality risk and are more likely to need advanced therapies (469, 570). Another specific patient population is infants with CDH as they have high rates of LV dysfunction even at birth, which impacts gas exchange and systemic perfusion in addition to the existing PH, and studies have shown that infants with CDH who have intact LV function might be more likely to respond to pulmonary vasodilators like iNO (207, 338).

RV-to-LV diameter ratio

While the RV is more compliant, the LV is better suited to handling a pressure overload. In PH, as RV pressures increase, the interventricular septum (IVS) starts flattening during systole, resulting in a “D-shaped” LV in the parasternal short-axis view (see Figure 8). In severe PH, where RV pressures are supra-systemic, the septum bulges out into the LV cavity at end-systole (308). This has been used to measure the RV/LV end-systolic diameter ratio, which has been shown to be significantly higher in children with PH compared to controls and correlates positively with adverse outcomes in pediatric PH (281). Flattening of the IVS offers indirect evidence of elevated pulmonary pressures in the absence of a TR jet, and end-systolic flattening of the IVS is a sensitive marker of RV systolic hypertension in pediatric PH (297). Severe septal flattening or bulging can also impact LV diastolic filling and in some situations lead to decreased cardiac output.

Systolic-to-diastolic duration ratio

The Doppler derived ratio of systolic to diastolic duration (S/D ratio) has been shown to be an indicator of RV dysfunction and is independent of heart size, hence valuable in the assessment of pediatric PH. Children with significant PH have marked decreases in their diastolic duration resulting in an increased S/D ratio, which progressively worsens with increasing heart rate. S/D ratio greater than 1.4 inversely correlated with survival in pediatric PH in one study (17).

Tissue Doppler velocities and three-dimensional (3-D) echocardiography

Tissue Doppler imaging (TDI) measures myocardial velocities, which is an estimator of RV systolic function. RV TDI correlates well with cardiac catheterization measurements in pediatric CHD patients with PH and has been used for follow-up of children with IPAH (281). TDI has been shown to accurately document reduced systolic and early diastolic RV velocities in infants with CDH and PH (465). TDI varies with age and heart rate, and hence normal values for adults cannot be applied to children. Also, adult studies have shown poor sensitivity of 33% but a 100% specificity in identifying precapillary PH (231). 3-D echo eliminates the need for geometric assessments and hence gives more accurate estimates of RV function and volume, which correlate with cardiac MRI estimated volumes in the pediatric population (363).

Evaluation of cardiac anatomy

During diagnosis and follow-up for PH, a careful evaluation of the entire cardiac anatomy and extracardiac structures including shunts, aortic coarctation, and pulmonary veins (PV) is important. Pulmonary vein stenosis (PVS) has been recently identified to be a risk factor for

developing severe PH in infants with BPD and is associated with a significant increase in mortality in these patients (141, 370, 575). What complicates this picture further is that PVS might develop over time or even after discharge from the NICU and is not evident often during the first imaging; one study showed that infants with BPD-PH received a median of five echocardiograms before they were diagnosed with PVS (370). Pulsed Doppler imaging of all pulmonary veins to look for PVS and either continuous, nonphasic flow, or absence of late diastolic flow reversal in the presence of nonphasic flow suggests PVS.

When echocardiograms of premature neonates were analyzed by blinded pediatric cardiologists who followed a standardized reading protocol, there was greater than 80% concordance on the diagnosis of PH, suggesting that the presence of a standardized protocol leads to a more consistent and accurate diagnosis of PH (381).

Cardiac catheterization

Cardiac catheterization remains the gold standard for diagnosis and monitoring of treatment response of pediatric PH. Catheterization helps to accurately confirm the diagnosis and severity of PH and to assess the response to pulmonary vasodilators (AVT). Catheterization is also needed to evaluate the response to vasodilator therapy, evaluate other diagnoses, and identify intra- or extracardiac conditions that affect prognosis such as left ventricular dysfunction or PVS, and to determine suitability for transplant. Ideally, every patient with an echocardiographic diagnosis of PH would be evaluated by cardiac catheterization at least once before starting therapy. However, this is not always feasible since infants and children undergoing catheterization require conscious sedation or general anesthesia, which increases the risk of adverse effects significantly. General anesthesia, which is preferred in infants and children younger than 12 years, provides a secure airway, a steady level of sedation, and control over gas exchange. However, it predisposes children to increased episodes of systemic hypotension, alters the pulmonary vascular hemodynamics, which might not be a representative of the true values during the awake state, and uses positive pressure ventilation, which might impair RV function (102). Although conscious sedation might avoid these side effects, it poses risks of developing hypoxia or hypercarbia, especially in the setting of lung disease or airway obstruction. Both induction and emergence from anesthesia have been identified as time points of increased risk, as well as any episodes of systemic hypotension or acute hypoxia as the RV is exposed to supra-systemic pressures. The risk of adverse events associated with catheterization range from 1.4% to 3.5% in pediatric PH, and mortality ranges from 0% to 1.4% (84,444, 445). This risk increases almost threefold in infants and children under the age of 2 (140). Risk factors for adverse events after catheterization include patient characteristics like prematurity, lower systemic arterial saturations or inotrope or systemic vasodilator treatment prior to catheterization, hemodialysis, and higher pulmonary vascular resistance and PAPs (444, 445). Centers with high volume of pediatric PH patients and catheterization numbers have lower rates of adverse events (445). Cardiac catheterization should be avoided in classic PPHN and should be postponed or even omitted in infants and children <2 to 5 kg who are at a higher risk of complications. It should also be avoided in acute presentation of PH or critically ill patients requiring immediate initiation of therapy (235). Having a pediatric pulmonary hypertension expert and a pediatric anesthesiologist and performing the procedure in a center capable of

postprocedural care of this vulnerable population in an intensive care setting are important for having better outcomes during and after the procedure.

The measurements obtained during cardiac catheterization include oxygen saturations, pressures in different chambers and vessels, systemic and pulmonary vascular blood flow, and AVT.

Oximetry—Blood sampling to determine oxygen saturation for calculation of flow should be performed both proximal and distal to the presence of shunts, if there are any. Occasionally, there are multiple sources of pulmonary blood flow (post-Fontan operation, for example); the true mixed PA saturation can be difficult to estimate and using cardiac MRI to quantify pulmonary and systemic blood flow is a better option in such cases (225). Obtaining the hemoglobin concentration during the time of the procedure is also important, as it affects the pulmonary vascular resistance and it is integral to the Fick equation (252).

Calculation of pressure, flow, and resistance—Systolic, mean and diastolic systemic arterial, RA, RV systolic and end-diastolic, systolic, mean and diastolic pulmonary arterial and bilateral pulmonary arterial wedge pressures are usually measured (25). Pulmonary arterial wedge pressure (PAWP) is indicative of LA pressures and LV dysfunction. Inability to obtain PAWP should prompt measurement of LA pressure and LV end-diastolic pressure. Ideal time point for obtaining measurements is end expiration in a spontaneously breathing patient and end inspiration in a mechanically ventilated patient. The Fick principle states that blood flow is proportional to the oxygen consumption (Vo_2) divided by the extraction of oxygen across the same vascular bed (169). Calculation of Vo_2 in real time and in real-life clinical settings is hard, especially in intubated patients. The breath-by-breath method for measuring Vo_2 correlated well with mass spectrometry measurements in pediatric cardiac catheterization but has not been validated in infants less than 3.5 kg (228). Systemic and pulmonary blood flows can be estimated using the Fick principle, and they can be used to calculate the vascular resistances. Both flood flow and resistance are usually then indexed to the body surface area. The Fick principle decreases in accuracy at high blood flows as the arteriovenous differences decrease. The thermodilution catheter method can also be used to estimate pulmonary blood flow if there are no intra or extracardiac shunts present.

Acute vasoreactivity testing (AVT)—AVT evaluates the response of the pulmonary vasculature to pulmonary vasodilators. It has two goals—(i) to assess prognosis and indication of PH-specific therapy and (ii) to assess the operability for PAH-CHD (4, 25, 355). True PAH acute responders (IPAH), when treated with calcium channel blockers, have an excellent prognosis with a 95% five-year survival rate (650). However, the long-term impact of defect closure in patients with CHD in the setting of PAH is unknown. Neonates with BPD-PH who underwent AVT with either 100% O_2 alone or in combination with iNO and had a positive response had better long-term outcomes compared to nonresponders (185). Hemodynamic and oxygen transport mechanisms are measured at the patient's baseline and then AVT is performed using iNO (20–80 ppm). In addition to iNO, 100% oxygen alone or in combination with iNO, aerosolized or intravenous PGI2 analogs, intravenous adenosine, and intravenous sildenafil have also been used (33, 49, 354, 531). The use of intravenous epoprostenol or adenosine is not recommended in the pediatric

population as data regarding optimal dosing are not well defined. In children with PH and elevated PVR, more acute responders were identified with iNO/O_2 combination than with O_2 alone, and although there was no difference in the responder rate between iNO alone and iNO/O_2 group, the latter showed improved pulmonary hemodynamics, which may warrant some caution during interpretation of results (49). Use of 100% O_2 alone should be avoided in patients with PAH-CHD, as this would lead to increased oxygen in the pulmonary venous blood and, consequently, the fraction bound to hemoglobin. This would lead to overestimation of pulmonary blood flow and hence an underestimation of the pulmonary resistance (25).

There are considerable differences between centers in identifying responders to AVT and selecting patients for treatment (157). The European Pediatric Pulmonary Vascular Disease Network suggests the use of the modified Barst criteria for AVT, whereas the recent 6th WSPH Pediatric Task Force recommends the use of the Sitbon criteria (4, 25, 235, 506).

Modified Barst criteria for AVT:

In patients with IPAH/HPAH: For patients without a shunt, a positive response to AVT is considered as a 20% decrease in mPAP and indexed PVR(PVRi)/indexed SVR(SVRi) ratio without a decrease in cardiac output.

In patients with PAH-CHD and shunts: The hemodynamic response defined as a positive response and operability in shunt defects (Qp:Qs > 1.5:1) is a >2% fall in the PVRi and PVRi/SVRi with respective final values <6 indexed WU (iWU) and <0.3.

Sitbon criteria: This is defined as the decrease in mPAP by at least 10 mmHg to a value of <40 mmHg with sustained cardiac output. If the mPAP is less than 40 mmHg to begin with, a drop by at least 10 mmHg without decrease in the cardiac output is defined as a positive AVT.

The Sitbon criteria were found to identify AVT responders who had better outcomes when treated with long-term CCBs (157, 548) and has been recommended by the latest WSPH Pediatric Task Force. It should be noted, however, that no fall in PAP does not necessarily mean no fall in PVR. Response to pulmonary vasodilators with a decrease in PVR and increase in Qp is possible without changes in the PAP, and hence hemodynamic indicators such as PVR/SVR and PVRi are considered better markers of AVT response.

Computed tomography (CT) scan

High-resolution computed tomography (HRCT) scan of the lung parenchyma along with computed tomography angiography (CTA) to evaluate the pulmonary, bronchial, and systemic thoracic vasculature is a commonly used tool in the diagnosis of neonatal and pediatric PH. Chest CT has significant utility in staging of pulmonary interstitial disease and in Group 3 PH due to lung hypoxia. CT with contrast and CTA can be used to rule out chronic thromboembolic pulmonary hypertensive disease. CT-measured ratio of main PA to ascending aorta of ≥1.3 raises the index of suspicion of PAH in children (235). Chest CT with CTA is also useful in identifying obstructive pulmonary vascular disease like peripheral pulmonary stenosis or pulmonary venous stenosis, which worsens mortality and morbidity in

BPD-PH. Lymph node enlargement, centrilobular ground-glass opacities, and septal thickening with pulmonary artery enlargement all point toward venous obstructive disease, whereas smooth interlobular septal thickening, diffuse multifocal ground-glass opacifications, and enlarged central pulmonary arteries are more indicative of pulmonary capillary hemangiomatosis (4). CTA can also identify systemic pulmonary collaterals that are present in up to 30% of infants with BPD-associated PH (141). These collaterals contribute to increased PAP, and closure of the collateral by interventional cardiologists may be needed to alleviate PH in select cases. It is also recommended that every patient undergoing evaluation for lung transplantation should receive a chest CT (329, 595).

Cardiac magnetic resonance imaging (CMRI)

Cardiac magnetic resonance imaging (CMRI) is recommended both as a part of the initial diagnostic workup and as a part of follow-up to assess ventricular function (333). CMRI is the gold standard to which all echocardiographic measures for evaluation of RV volume and function are compared (524, 616). CMRI is usually performed in infants and children with either some degree of sedation or under general anesthesia, which again pose similar risks as stated above during cardiac catheterization (584). CMRI helps in reliable assessment of the RV and LV size and volume indices as well as the RV ejection fraction (RVEF). RVEF and LV stroke volume were found to be most strong predictors of death or need for heart transplant in pediatric PH (2.6- and 2.5-fold increase in mortality for every 1-SD decrease, respectively) out of all variables measured by CMRI (402). It is recommended that all pediatric CMRI should include cine CMRI, which is the gold standard for assessment of biventricular volumes, muscle mass, and global pump function (226, 291). In addition, selective blood flow measurements in pulmonary and systemic circulation and quantification of shunt flow can be performed with increased accuracy. CMRI when performed in preterm neonates found that when controlled for BPD severity, birthweight and gestational age, MRI LV eccentricity index and PA/aorta ratio correlated positively with the need for PH therapy either during hospitalization or after discharge (130). Other parameters for which CMRI is used are visualization of myocardial fibrosis using late gadolinium enhancement, strain and strain rate, septal curvature, pulmonary artery stiffness, and RV-PA coupling (67, 90, 333). MR angiography is also useful for evaluation of any pulmonary venous thromboembolism.

Ventilation/perfusion scan (VP scan)

Ventilation perfusion mismatch in a patient with known or suspected PH raises concern for thromboembolic disease of the pulmonary vasculature. This is especially important in IPAH as well as in known Eisenmenger’s syndrome due to the increased incidence of thromboembolic disease in these patients (76). Chronic thromboembolic PH shows areas of ventilation-perfusion mismatch in VP scans, usually one area, sometimes two or more (177, 415).

Biomarkers

Brain natriuretic peptide (BNP) and its precursor, NT-proBNP, are the most studied biomarkers in both adult and pediatric PH (83). A recent meta-analysis of pediatric PH biomarkers found that low levels of NT-proBNP are strong predictors of survival and children who stay at NT-proBNP levels below 1200 ng/L during treatment have significantly

better survival rates, a statistic that has been shown to be true in adult PH as well (438, 475, 477). BNP has a shorter half-life than NT-pro-BNP; hence the latter is more commonly used, although it is more susceptible to changes in renal function. Reference values of NT-proBNP have been established for the pediatric population and increase in the first few days after life and then fall drastically after the first week, and then gradually throughout childhood (440). Recently, urinary NT-pro-BNP has also been studied as a screening tool for PH in preterm infants (425). A proteomic analysis of early serum angiogenic proteins showed that early increases in bone morphogenetic protein 10 (BMP10) are strongly associated with late increases in BPD and PH (28). A decrease in cord blood angiogenic factors associated with placental maternal vascular under-perfusion has been also associated with an increased risk of BPD-PH in preterm neonates (387). MicroRNAs, which have recently acquired a great deal of attention as biomarkers for diseases in which angiogenesis is impaired, have shown some promise in predicting pediatric PH (296). Circulating endothelial cells (CECs) and endothelial cell progenitors (ECPs) have been shown to be present in blood of PH patients (124, 360, 549). Measurement of CECs in children with IPAH and CHD-PAH before and after treatment showed that rising levels of CECs preceded clinical deterioration (346). Furthermore, elevated CEC levels were associated with irreversibility in CHD-PAH (550). Several other biomarkers such as uric acid, atrial natriuretic peptide, and Troponin T have also been shown to be associated with worse outcomes in both adult and pediatric PH (4).

Genetic testing

Genetic mutations are increasingly being identified in children with IPAH/HPAH, with BMPR2 being the most common (almost 70% of HPAH and 10%–40% of IPAH cases) (15, 347). With the emerging recognition of the need for genetic testing, other genes have been found to be involved in pediatric PAH, including, but not limited to, ALK1, ABCC8, ENG, CAV1, KCKN3, EIF2AK4, and TBX4 (7, 35, 188, 347, 367, 411). Genetic testing for these commonly found genes is currently recommended for families of all children diagnosed with IPAH/HPAH. Gene testing for less implicated genes in PAH such as NOTCH3, SMAD9, GDF2, AQP1, SMAD8, SOX17, and ATP13A3 can be performed as a second-tier test in children with PAH of unknown cause with a negative test for the previously mentioned genes (235). Next-generation sequencing should be preferably performed to maximize the depth of coverage for the affected genes. Most PAH-associated mutations are inherited in an autosomal dominant fashion with incomplete penetrance. Hence, first-degree relatives of all PAH patients with a genetic mutation known to be implicated in PAH should at least undergo genetic counseling. Children who are found to have PAH-associated mutations and are asymptomatic should undergo screening echocardiograms every 1 to 3 years to detect elevated RV pressure, and asymptomatic first-degree relatives of patients with PAH-associated mutations should undergo PH screening if they develop new cardiorespiratory symptoms (4, 235, 506).

Six-minute walk test (6MWT)

The six-minute walking distance (6MWD) is considered a useful tool for follow-up and as a therapeutic endpoint for treatment goals in pediatric PH. In adult PH, the 6MWD correlates well with other parameters of disease severity like the WHO-FC, and the magnitude of oxygen desaturations during the test and the heart rate recovery after it have been used for

prognostication of adult PH (393, 456, 490). Studies have shown that it is feasible to perform the 6MWT in children and that it reflects disease severity and clinically relevant exercise tolerance (156, 198, 330). The 6MWD is higher in children than in adults, and reference values have been established for the pediatric population (330). Shorter 6MWD combined with lower transcutaneous oxygen saturations during the 6MWT correlated with higher WHO-FC and NT-proBNP levels and worse transplant-free outcomes in pediatric PH patients in one study (156).

Cardiopulmonary exercise testing (CPET)

CPET is performed to both evaluate and follow up patients with PH. Adult studies have shown that low peak oxygen uptake and low systolic blood pressure at peak of exercise in patients with PH undergoing CPET correlate with impaired survival (632). CPET has been shown to be feasible and safe to perform in children with decreased peak oxygen uptake and decreased baseline oxygen saturation at peak exercise compared to healthy controls (8, 551). The peak oxygen uptake has also been shown to strongly correlate with invasive measures of disease severity, including the pulmonary vascular resistance index. The type of exercise, treadmill versus cycle ergometer, or the specific exercise protocol is not important to the success of the test if the protocol has been standardized and is performed in a controlled environment. Changes in oxygen consumption, CO_2 production, minute ventilation, heart rate, and blood pressure should be obtained at rest, during exercise and during recovery. Subtle changes in exercise tolerance may suggest deterioration prior to clinical manifestations, which might prompt earlier reevaluation including cardiac catheterization (198).

Treatment

The 6th WSPH Pediatric Task Force has proposed a treatment algorithm based on expert consensus opinion and is mostly relevant for the treatment of pediatric IPAH/HPAH (Figure 9). Similar algorithms exist for the treatment of BPD-PH (Figure 10), which are based on expert consensus opinion. There is a lack of randomized clinical trials evaluating therapies in the pediatric PH population, and most data are based off extrapolation from adult trials or case series from off-label use.

Oxygen therapy

Maintaining adequate oxygenation is key to preventing the vicious cycle of hypoxic pulmonary vasoconstriction and the VP mismatch and hypoxemia that ensues (629). The effect of oxygen on pulmonary vasodilatation increases with increasing gestational age (110, 494). Extremely preterm neonates have diminished pulmonary blood flow with a poor vasodilatory response to oxygen. During resuscitation of these infants, 100% oxygen decreases the PVR rapidly; however, this effect is not sustained and might lead to blunted responsiveness to iNO later and increased oxygen toxicity from free radicals (109, 110). To answer the question of the optimal target oxygen saturation for extremely premature infants, several randomized clinical trials were conducted, and these were recently studied in a meta-analysis called the Neonatal Oxygenation Prospective Meta-analysis (NeoPROM) (36, 134, 436, 528, 529). These studies did not measure PH as an outcome measure but did document

a higher mortality risk when preterm infants were randomized to lower oxygen saturations (30). Observational cohort studies have shown that changing the oxygen saturation parameters for preterm neonates from lower (tolerating a lower limit of up to 85%) to higher (at least above 90%) targets decreased the incidence of elevated PVR and PH at 36 weeks postmenstrual age in these infants (288, 327). This comes as a trade-off since the incidence of BPD was found to be higher in the Neonatal Research Network units after the saturation target parameters were changed to higher levels (182). In preterm infants with BPD-PH, minor episodes of desaturations increase pulmonary pressures and should be avoided (3, 6, 417). A recent consensus from the PPHNet recommends maintaining oxygen saturations between 92% and 95% in these infants and use of chronic supplemental oxygen before starting pharmacological vasodilators (320). The European PPVDN recommends target oxygen saturations of >93% in preterm neonates and >95% for neonates with an echocardiographic diagnosis of BPD-PH (246). In PPHN, although increased oxygen is usually required to reverse the pulmonary vasoconstriction and hypoxemia, acute hyperoxia should also be avoided as it increases oxidant stress, alters pulmonary vasoreactivity, and augments pulmonary vascular dysfunction associated with lung disease (564). Exposure to prolonged hyperoxia and high oxygenation indices prior to start of iNO was associated with a higher incidence of ECMO and/or death in several clinical trials (109). Therefore, maintaining a strategy to minimize oxygen exposure with lung recruitment, surfactant administration and iNO are essential to reduce the toxic effects of free radical damage in PPHN (564).

For the treatment of PAH in the intensive care unit as well as at home in PAH or CHD-PAH population, it is advisable to use continuous supplemental oxygen to keep oxygen saturations >95% or the arterial pO_2 above 60 mmHg (227). These parameters change during shunt physiology. For patients with CHD-PAH and significant left-to-right shunt, oxygen therapy might lead to pulmonary overcirculation, which may worsen the right heart function without lowering the mPAP in the long term. For patients with right-to-left shunts, maintaining the shunt flow may be critical in maintaining adequate systemic oxygen delivery. Hence, oxygen is not indicated unless there is parenchymal lung disease or there is profound cyanosis (75%-85% are acceptable saturation parameters in these children) (285).

Diuretics and fluid balance

Fluid and volume status need delicate balancing in PH. In neonates and children with severe PH, the RV is preload dependent and volume depletion can lead to acute worsening and PH crises. However, severe PH by itself leads to RV failure, volume overload, increased central venous pressure, hepatic congestion, ascites, and peripheral edema. There have been no randomized trials to study the effect of diuretic use on PH outcomes, either in adults or in children. Hence, current recommendations are to limit the use of diuretics to loop diuretics and aldosterone antagonists in patients with the signs of systemic venous congestion or severe left-to-right shunting causing pulmonary overcirculation (439). Aldosterone antagonists such as spironolactone and eplerenone block mineralocorticoid receptor action and have been shown to improve RV and LV function in adults, but pediatric data are lacking (85, 138). It is important to monitor electrolyte levels while on diuretics, and to carefully monitor fluid status as the RV is preload dependent in such situations. Infants with BPD-PH

are often on chronic diuretics to reduce pulmonary vascular congestion from the sequelae of BPD. This, however, leads to a chronic low-volume state and might mask left ventricular dysfunction, which can be a cause of PH in these patients. These patients might be given a small fluid bolus during cardiac catheterization to evaluate the left ventricular function when subjected to an increased afterload (320).

Digoxin

Digoxin or digitalis has been shown to acutely improve cardiac output in adult IPAH patients and slow the ventricular rate down in PAH patients with tachyarrhythmias (499). There are no studies on the long-term effects of digoxin on the right ventricular function, and as such it is not a drug commonly recommended in pediatric PH.

Acid-base balance

Acidosis increases PVR and causes pulmonary vasoconstriction and may impede the action of inotropes (111). Therefore, acidosis should be avoided, and attempts should be made to normalize the arterial pH. Alkalization is effective for the treatment of acute PH crises in the intensive care unit (111, 285, 412). In the era before the use of iNO, alkalization was induced in newborns with PPHN with serum bicarbonate infusions. Although alkalization brings about a transient decrease in PVR and improvement in oxygenation, animal models have shown an exaggerated pulmonary vasoconstrictive response to hypoxia after prolonged alkalosis (516). Alkalosis also causes cerebral vasoconstriction and diminished cerebral blood flow and has been shown to worsen neurodevelopmental outcomes and hearing deficits in newborns and thus should be strongly avoided (376).

Anticoagulation

Children with PH are often on anticoagulants or antiplatelet agents. There are no long-term data on the benefit of children on chronic anticoagulation, but the current consensus is that it may benefit certain classes of pediatric PH such as progressive IPAH/HPAH, chronic thromboembolic PH, hypercoagulable states, and patients in low cardiac output states, which predispose to blood stasis and increased coagulability (235). The target international normalized ratio in IPAH/HPAH is between 1.5 and 2.0; however, this is an empirical target (4). Anticoagulant and antiplatelet therapy should be avoided in patients with hereditary hemorrhagic telangiectasia (HHT) and porto-pulmonary hypertension and should be critically reviewed in smaller children who are at a higher risk for hemorrhagic complications and congenital or acquired von Willebrand disease. A class of pediatric PH that is at a higher risk for pulmonary vascular thromboses are children with Eisenmenger's syndrome, but they are also at a higher risk of severe pulmonary hemorrhage and hence the use of anticoagulation in them warrants caution. A retrospective study of adults with Eisenmenger's syndrome on anticoagulants showed no impact of anticoagulant use on long-term survival (523).

Inhaled nitric oxide (iNO)

iNO is one of the most used therapies to treat PH in the acute setting of PPHN, PH in CDH, acute postoperative PH or PH crises. It has been approved by the FDA since 1999 as a

pulmonary vasodilator therapy for the treatment of PPHN in term and near-term infants, based on two landmark multicenter placebo-controlled randomized controlled trials that showed a significant decrease in the need for extracorporeal membrane oxygenation (ECMO) in the iNO group (120, 435). It is delivered as an inhaled gas blended with air or oxygen and simulates the action of endogenous NO to activate sGC in the pulmonary arterial smooth muscle cells, leading to increased cGMP levels and SMC relaxation. NO can cross the alveolar-capillary membrane to enter the smooth muscles of the precapillary pulmonary arterioles, causing selective vasodilation and attenuation of vascular remodeling (306). iNO has a relatively short half-life of 15 to 30 s and is rapidly metabolized by Hb in the RBC in the pulmonary circulation, preventing its systemic effects (51). Chronic use of iNO is associated with methemoglobinemia, and hence methemoglobin levels should be monitored in these patients (496, 590). iNO is usually started at a dose of 20 parts per million (ppm) regardless of the etiology. Higher doses do not improve oxygenation and contribute to increased risks of methemoglobinemia and NO_2 exposure. Once oxygenation improves, iNO dose can be rapidly weaned off in steps to 5ppm and then gradually weaned in 1 ppm decrements to 1 ppm before discontinuation. There are reports of life-threatening rebound PH after discontinuation, and this can usually be prevented by slow weaning from 5 to 1 ppm and waiting for a few hours for clinical stability before turning it off (136).

The use of iNO in term and near-term infants for the treatment of PPHN is well studied and documented through several double-blinded placebo-controlled trials (44, 135, 137, 180, 303, 358, 435, 520, 633). There have also been several trials in term and near-term infants with PPHN who have been randomized to either iNO or placebo and compared infants based on their severity of respiratory failure as determined by the increased oxygenation index or alveolar-arterial oxygen gradient (44, 126, 217, 316). A randomized trial also found that starting iNO at an earlier oxygenation index (15–25 vs >25) does not decrease mortality or the need for ECMO (316). A 2016 Cochrane review for the use of iNO in term and near-term infants with hypoxic respiratory failure studied 17 randomized controlled trials and found that iNO improved outcomes in hypoxic term and near-term infants by reducing the combined endpoint of death or need for ECMO, which was primarily due to the reduction in the use of ECMO (47). iNO also showed an improved oxygenation index within 30 to 60 min of start of the drug and improved arterial oxygen saturation, and these improvements are not limited to those who show echocardiographic signs of decrease in PAPs (47).

A unique population with PPHN is the CDH population, where in addition to altered pulmonary vasoreactivity, pulmonary hypoplasia and associated left ventricular dysfunction often complicate the presentation and management. The only two randomized trials studying the effects of iNO in infants with hypoxic respiratory failure due to CDH and PH were the NINOS 1997 trial and the diaphragmatic hernia subpopulation of the Clark 2000 trial (120, 467). Both these trials found that death or need for ECMO did not change either separately or as a composite outcome in infants with CDH who were randomized to either placebo or iNO. Two other large-scale database studies from the Pediatric Health Information System (PHIS) and from the CDH Study Group (CDHSG) were conducted to evaluate the use of iNO in CDH (100, 483). The PHIS data showed that out of 1713 neonates with CDH in the United States, 57% of the infants received iNO and that only half of these infants showed an improvement in oxygenation. However, there was no change in mortality or need for ECMO

for these infants (100). The CDHSG data, which included over 3300 infants from 13 different countries, showed that 74% of the infants who received an echocardiographic diagnosis of PH in the first week of life were started on iNO. The infants who were diagnosed with PH were also more likely to need ECMO, but iNO did not change the need for ECMO or the mortality for this cohort (483). A recent single-center retrospective review of infants with CDH who were started on iNO either due to clinical hypoxemia or an echocardiographic diagnosis of PH found a subset of patients who responded to iNO (338). Responders were less likely to have left ventricular systolic dysfunction and were less likely to need ECMO. Current recommendations from the AHA allow the use of iNO in infants with CDH and normal left ventricular function but advise against continuation for more than 24 h if no clinical benefit is seen (4).

iNO has also been studied for preterm infants with hypoxemic respiratory failure as an initial rescue therapy, as a routine adjunct to conventional ventilatory support, or as a later treatment in infants at risk for BPD (4, 42, 133, 240, 298, 304, 386, 530, 560, 571, 572, 605, 627). These studies were heterogeneous for the birthweight and gestational age of infants recruited as well as the eligibility criteria. There was no effect of iNO on death before 36 weeks postmenstrual age or death before discharge or on BPD at 36 weeks postmenstrual age (46). However, there is a subpopulation of infants with oligohydramnios and/or preterm premature prolonged rupture of membranes who have shown improved oxygenation and pulmonary hemodynamics, and a recent expert panel recommended use of iNO in this cohort (298, 299 301).

iNO is also used in acute postoperative PH and in PH crises in acute care settings as well as during cardiopulmonary bypass for congenital heart surgery (63, 113). Currently, a multicenter randomized trial to evaluate the benefits of iNO during the entire duration of cardiopulmonary bypass in CHD surgery is underway and results are awaited (527).

Phosphodiesterase-5 (PDE-5) inhibitors

Sildenafil and tadalafil are the PDE-5 inhibitors that have been used in the pediatric population. PDE-5 degrades cGMP, which is responsible for pulmonary vascular smooth muscle relaxation. Sildenafil was initially studied as a candidate drug for the treatment of angina pectoris in the 1980s. Urologic studies at the same time showed that cGMP was also responsible for smooth muscle relaxation and vasodilatation leading to penile erection; hence use of sildenafil started in the treatment of erectile dysfunction (ED) and was approved by the FDA for ED in 1998 (205, 215, 408). As the role of PDE-5 in the lung vasculature became more evident in the 1990s, sildenafil was studied for adult PH and the first intravenous placebo control study was performed in late 1990s, which showed that sildenafil selectively reduced pulmonary pressure and pulmonary vascular resistance in patients with PAH, pulmonary venous hypertension, and hypoxic pulmonary hypertension (205). This led to the approval for the use of oral sildenafil in adult Group 1 PH in 2005 by the US-FDA, and later in 2009 the intravenous formulation was also approved.

Sildenafil is a water-soluble compound that has a similar half-life in the pediatric population compared to adults, although the volume of distribution and the peak concentration reached are higher in children (449). An open-label trial of intravenous sildenafil in term neonates

with PPHN found similar results with fourfold higher volume of distribution; however, this population also had significantly longer plasma half-life. This decreased with increasing clearance and reached adult values by one week of life, attributed to the postnatal maturation of N-demethylation mechanism in neonates (420). Oral bioavailability of sildenafil is ~40% and it undergoes first-pass metabolism in the liver by the hepatic cytochrome P450 pathway (261). For children weighing above 20 kg, the recommended dose is 20 mg three times daily (TID) and for 8–20 kg it is 10 mg TID as per European guidelines (149). The common practice for infants and children weighing below 8 kg is to start at 0.5 mg/kg every 8 h and escalate to 1 mg/kg every 8 h, which is continued as the maintenance dosing for oral sildenafil at most PH centers (123). There have been multiple case series and small studies on the use of both oral and intravenous sildenafil in pediatric PH, which included CHD-PAH, PPHN, postoperative PH, BPD, and CDH (43, 183, 210, 212, 247, 263, 407, 434, 460, 546, 563, 601, 602). Sildenafil has been shown to be useful in prevention and treatment of postoperative PH in children after CHD surgery, either as an adjunct to iNO or to help weaning from it (34, 432). A recent meta-analysis of perioperative PH in children with CHD found that sildenafil decreased ICU stay significantly, although it did not decrease total length of stay or mortality before discharge (278). For PPHN, intravenous sildenafil was associated with immediate and sustained improvements in oxygenation in those infants who received higher infusion doses (563). A recent Cochrane review that analyzed 5 trials where sildenafil was used for the treatment of PPHN found a significant decrease in mortality when sildenafil was compared to placebo; however, the differences ceased to exist when compared to iNO or when iNO was used in both groups (294). Recently, a multicenter international trial has started recruiting patients with CDH and PH to be randomized to intravenous sildenafil infusion or iNO; the outcomes are absence of PH by day of life 14 or death at day of life 28 (122). The first randomized, double-blinded, placebo-controlled trial of oral sildenafil monotherapy in children with PAH was the STARTS-1 trial (Sildenafil in Treatment-Naïve Children, Aged 1 to 17 years, with PAH), which randomized children >8 kg to either low-, medium-, or high-dose sildenafil or placebo for 16 weeks and peak oxygen consumption (PVO_2) was measured during CPET. Although this study found that PVO_2 was only marginally changed in the sildenafil groups combined together, when medium- and high-dose groups were combined, they showed efficacy in PVO_2, WHO-FC, and hemodynamic parameters (55). When these groups were followed in the long term as a part of STARTS-2 trial, they showed increased mortality with higher doses of sildenafil for unexplained reasons (50). This led to the issuance of a US-FDA warning in 2012 against the use of sildenafil in the treatment of pediatric PH, which requires closer monitoring and surveillance of patients on sildenafil (5, 380). A multivariate analysis of the STARTS-2 trial data had shown that the increased mortality was primarily associated with HPAH, high PVRI, and high RA pressures, and adjusting for these factors decreased the hazard ratio for high-dose versus low-dose sildenafil. The latest FDA recommendations for sildenafil use in pediatric PH issued in 2014 do not recommend against the routine use of sildenafil and recommend closer monitoring of children on long-term sildenafil, especially on higher doses (149).

Tadalafil is another selective PDE-5 inhibitor that has once daily dosing and a longer half-life than sildenafil and has been shown to improve exercise capacity and quality of life

measures in adults with PH. It was studied in children with PH either as an initial drug or as a transition from sildenafil and was shown to improve mPAP and PVRI in both cases (579). An Iranian pediatric PH cohort also reported similar findings after transitioning to tadalafil from sildenafil with no worsening in the NYHA FC or pulmonary hemodynamics (519). Postmarketing surveillance in Japan has shown that tadalafil is safe and effective as monotherapy in pediatric PH (639).

Udenafil is a newer selective PDE-5 inhibitor having a longer duration of action and was found to improve myocardial performance in pediatric patients with Fontan physiology in a phase I/II clinical trial conducted by the Pediatric Heart Network (213). Patients with Fontan physiology have a circulation that is dependent on low pulmonary vascular resistance to maintain adequate cardiac output; hence the patients enrolled in this trial did not have traditional parameters of PAH. This study was subsequently extended to a multicenter international trial (Fontan Udenafil Exercise Longitudinal trial) and found no difference in the myocardial performance index. Udenafil use was not associated with improvements in peak oxygen consumption during exercise, but it was associated with improvements in several measures of exercise performance at the ventilatory anaerobic threshold (214).

Calcium channel blockers (CCBs)

CCBs are used infrequently in children with PAH as first-line therapy; however, it is efficacious in children who are AVT responders (592). Based on the Sitbon criteria, those children with IPAH or HPAH who respond to NO or 100% oxygen during AVT (around 8%-15% of children with IPAH), it is prudent to offer CCBs as first-line monotherapy (593). AVT establishes a relative contribution of reversible vasoconstriction versus fixed stenosis in children with PAH (593). Those who have a negative AVT are unlikely to benefit from CCBs, and additionally may have deleterious adverse reactions (498, 547). CCBs are not meant to be used in pediatric PAH without a prior documented positive response to AVT as they can cause systemic hypotension, worsen right heart failure, and potentially lead to death (53, 194). The reasons for such effects range from depression in the myocardial contractility and negative inotropic effects to the activation of renin-angiotensin system and hypotension, leading to decreased coronary perfusion and myocardial dysfunction from ischemia (457, 593). Those children who respond to CCBs as initial monotherapy can be continued on them with close follow-up, keeping in mind that they can become unresponsive and deteriorate later, necessitating further evaluation and addition of other drugs (235, 650). It should also be kept in mind that children with PAH and a significant intracardiac left-to-right shunt or those with Eisenmenger’s syndrome most likely will not benefit from CCB therapy regardless of the AVT and hence CCBs should not be used in this setting (235). CCBs are also not indicated in infants less than 1 year of age as the negative inotropic effects are pronounced in this age group. The CCBs used in pediatric PAH are nifedipine (2-5 mg/kg/day), diltiazem (3-5 mg/kg/day), and amlodipine (2.5-10 mg/day) (37). Diltiazem lowers heart rates more prominently than the other ones affecting cardiac output and systemic blood pressure; hence it is preferred in children who have higher resting heart rates. Verapamil is also contraindicated in PAH due to its tendency to cause bradycardia without significant pulmonary vasodilatory properties (4).

Prostacyclin analogs

PGI2 analogs, which fall in the larger group of prostanoids, mimic endogenous PGI2 and stimulate G-protein-coupled receptors on the surface of endothelial and smooth muscle cells to increase intracellular cAMP levels, which result in pulmonary vasodilatation and decrease in PVR. There is an imbalance in the favor of vasoconstrictive thromboxane A2 instead of vasodilatory PGI2 in PAH. PGI2s are FDA-approved in adults with PAH and are used off-label in the pediatric PH population as monotherapy in those who are in high-risk PH group and fail AVT or those who do not show any improvement on CCBs after a positive AVT. They are also used as combined therapy in pediatric PH patients who are in low-risk PH group but fail to improve on monotherapy of PDE-5 inhibitor or ERAs (235). The three PGI2s used in the pediatric population are epoprostenol, iloprost, and treprostinil.

Epoprostenol is the first prostanoid to be FDA approved and is still the gold standard of treatment for severe PH. It has a very rapid onset of action and a short half-life; hence it is preferably given as a continuous intravenous infusion. In acute postoperative PH as well as in neonates with severe PH from BPD, CDH, or PPHN, intravenous epoprostenol can be used as an alternative if iNO is unavailable. Multiple small studies and retrospective data have shown improved survival and quality of life in adult and pediatric PAH treated with intravenous epoprostenol (56, 272, 540, 650, 660). A cohort of 77 children with IPAH on epoprostenol who were followed through the 1990s to early 2000s showed survival of 94%, 81% and 61% at 1, 5, and 10 years, respectively (650). In neonates with PPHN refractory to iNO, a subpopulation responds to intravenous epoprostenol with a decrease in the oxygenation index and need for ECMO (13). There is a need to study the use of prostanoids in the treatment of PPHN using randomized trials as was pointed out by a recent meta-analysis (538). The side effects of epoprostenol include headache, gastrointestinal disturbances, jaw pain, bradycardia, hypotension, and thrombocytopenia. Epoprostenol when given to patients with parenchymal lung disease such as BPD and interstitial lung disease may lead to worsening of ventilation perfusion matching. In patients with veno-occlusive disease and PVS, epoprostenol can lead to worsening of pulmonary edema. It can also affect platelet counts and lead to an increased risk of bleeding (167). Inhaled epoprostenol has been used recently in acute care settings for PPHN where iNO might be unavailable or infants are unresponsive to iNO and has been shown to improve oxygenation and echocardiographic parameters of PH significantly (72).

Iloprost is a synthetic PGI2 analogue approved by the FDA for adult PAH in 2004. It has a short half-life of 20 to 25 min, longer than epoprostenol. The benefit of aerosolized iloprost over other prostanoids is that it lowers PVR but does not affect systemic blood pressure. Like epoprostenol, iloprost has also been used as an adjunct or in place of iNO in acute postoperative PH and in PPHN, where it lowers mean pulmonary pressure and improves oxygenation (356). A retrospective study of the use of inhaled iloprost in IPAH and CHD-PAH in the pediatric population showed that it was effective and well tolerated in this population (409). Similarly, another retrospective study of inhaled iloprost in preterm neonates with severe respiratory distress syndrome and PPHN showed benefits with improved oxygenation and with no systemic hypotension (645). There are other smaller studies where iloprost has been used in conjunction with oral sildenafil or bosentan for the

treatment of pediatric PH (132, 421, 545). In both IPAH and CHD-PAH, inhaled iloprost has been shown to improve the functional status when studied in the long term (273). One major drawback of the use of inhaled iloprost in the pediatric population is that it needs to be administered using nebulization every 6 to 8 h and requires patient compliance, which might be difficult in a population already facing a lot of quality of life challenges (273, 450). There have also been reports of worsening reactive airway disease on inhaled iloprost (273).

Treprostinil is another PGI2 analogue approved for use as oral, inhaled, intravenous, and subcutaneous forms. This has a longer half-life (steady state in 10 h) compared to other prostanoids and is stable at neutral pH at room temperature and hence can be given as continuous infusion. Subcutaneous mode of delivery avoids problems associated with central lines; however, it causes pain and reactions at the infusion site. Adults with PAH on long-term intravenous or subcutaneous treprostinil have displayed good long-term results (52, 216). There have been reports of pediatric patients on intravenous epoprostenol who were transitioned over to intravenous treprostinil due to the longer half-life of the latter, and these patients had no change in exercise capacity, WHO-FC, hemodynamics, and echocardiographic determination of right ventricular systolic pressure. The side effects associated with epoprostenol of headache, rash, diarrhea, and jaw pain have decreased on treprostinil (271). Intravenous treprostinil is also associated with catheter-associated infections, but these can be decreased by protecting catheter connections, avoiding water on any connection and a more basic buffer (155, 184). Subcutaneous treprostinil has also been used in pediatric and neonatal PH and has been well tolerated and efficacious (178). Inhaled treprostinil is available as well; however, it achieves lower plasma concentrations than the subcutaneous or intravenous forms and hence should not be used in patients who are not responding to the maximal doses of parenteral treprostinil (167). Inhaled treprostinil reaches peak levels in 5 to 10 min and needs to be administered every 4 to 6 h. Oral treprostinil, although approved in adults, has not been studied in the pediatric population much, primarily since the tablet cannot be crushed and there is no oral suspension available (167). Treprostinil clearance is decreased in patients with liver disease, and coadministration with anticoagulants or other vasodilators may increase the risk of bleeding and systemic hypotension.

Beraprost is an oral PGI2 analog that has not been approved in the United States or Europe and has not been well studied in children. A double-blinded, placebo-controlled, randomized trial of beraprost in adult PAH showed improved hemodynamics initially; however, this was not sustained over a long period (57).

Endothelin antagonists

Endothelin receptor antagonists (ERAs) are now considered first-line oral pharmacotherapy in pediatric IPAH/HPAH patients who either have a negative AVT and are low risk based on risk stratification or those who did not show sustained and improved reactivity on oral CCBs after a positive AVT (4). As described in a separate section, ET-1 acts on both ETA and ETB, which are G-protein-coupled receptors present on smooth muscle cells and endothelial cells. ETA binding leads to increased intracellular Ca^{2+} causing vasoconstriction, whereas ETB stimulation leads to the release of NO and PGI2, increased ET-1 clearance and a minor

effect on pulmonary vasodilatation, and reduced pulmonary vascular remodeling (65, 160). The ERAs used in clinical medicine for PH include bosentan, ambrisentan, and macitentan.

Bosentan is a nonselective ERA and inhibits binding of ET-1 to both ETA and ETB receptors and has been shown to improve exercise capacity and pulmonary vascular hemodynamics in adults with PAH (112). Pharmacokinetics of bosentan in pediatric PAH and adult patients are similar with a ~50% oral bioavailability and half-life of 5.4 h (54). It is metabolized by the liver isoenzymes, CYP3A4 and 2C9, and is a potent CYP3A4 inducer. Thus, other drugs that are metabolized by CYP3A4 like sildenafil need to be dose adjusted when bosentan is coadministered (618). Bosentan also elevated liver enzymes and has been shown to cause cirrhosis with chronic use. Hence, monthly monitoring of liver enzymes is important while on bosentan (618). It has been listed by the FDA as an indication for children aged three years and older with IPAH/HPAH at a dose of 2 mg/kg twice a day (618). Small prospective cohort studies and retrospective reviews have found bosentan to improve the 6MWD, decrease mPAP and PVR in pediatric patients with IPAH (250, 371, 401, 493). Bosentan, in conjunction with or independent of other PAH-specific therapies, showed improved survival in children with IPAH at 1, 2, 3, and 4 years of 98%, 88%, 82%, and 82%, respectively (274). FUTURE-1 (pediatric formulation of bosentan in PAH), which enrolled 36 patients and followed 33 of them to the FUTURE-2 trial, showed that the pediatric bosentan formulation was well tolerated and its safety profile was comparable to that of the adult formulation when used in children (70). The FUTURE-1 trial had shown that dosing of 2 mg/kg twice a day versus 4 mg/kg twice a day yielded similar concentrations of bosentan in the plasma (64). A third pharmacokinetic study looked at 2 mg/kg three times daily versus twice daily dosing of bosentan in pediatric PAH and found no clinically relevant difference in exposure to bosentan or safety profile between the two, and hence current recommendations are to use 2 mg/kg twice daily (71). For older children, the dosing recommendations for bosentan are based on the BREATHE-3 trial: 31.25, 62.5, and 125 twice daily for 10 to 20, 20 to 40, and >40 kg, respectively (37, 54, 103). Bosentan was found to significantly improve the oxygenation index and decrease PAPs in newborns with PPHN compared to placebo without noticeable side effects in a single-center study done in a setting where iNO was not available (399). However, when bosentan was used as an adjunct in newborns with PPHN on iNO (FUTURE-4 trial), it did not improve oxygenation or other outcomes compared to placebo, and there was no difference in time to weaning from iNO or mechanical ventilation from both groups (562).

Ambrisentan is a selective ETA receptor antagonist, requires once-daily dosing, and has a half-life of around 9 h. Ambrisentan also does not affect liver enzymes; hence they do not need to be monitored as in bosentan therapy. Ambrisentan has been approved by the FDA for the treatment of adult PAH and in two multicenter adult trials (ARIES-1 and ARIES-2) was found to improve the 6MWD and delay clinical worsening (193). A retrospective study of ambrisentan use in children with PAH as an add-on therapy to or as a transition from bosentan found improved mPAP and WHO-FC in the cohort, with 13% of patients discontinuing ambrisentan due to severe headache, lack of efficacy, or near-syncopal events (580).

Macitentan is another nonselective ERA; however, it has greater affinity for ETA receptors. Long-term macitentan therapy in adult patients with PAH was associated with significant reductions in morbidity and mortality compared to placebo (SERAPHIN trial) (482, 555). A current multicenter, open-label, phase III trial to study the pharmacokinetics and long-term effects of macitentan in pediatric PAH is underway (167).

Soluble guanylate cyclase stimulators

This class of drugs acts along the NO-cGMP pathway and increases the intracellular concentration of cGMP in the smooth muscle cells, leading to the downstream cascade of smooth muscle relaxation. Adult patients with chronic thromboembolic PH when treated with riociguat showed improvements in exercise capacity and PVR (203, 541). Adults with PAH who were either treatment-naïve or were pretreated with ERAs or prostanoids when started on riociguat showed improvements in several clinically relevant endpoints, including WHO-FC and exercise capacity (204, 514). When a subpopulation of these adult PAH patients with CHD were analyzed, they were also found to display similar improvements in exercise capacity and WHO-FC, which were sustained at the two-year follow-up (505). A case report of a child with severe PAH with supra-systemic PVR who had failed treatment with amlodipine, bosentan, and sildenafil showed sustained improvement in PVR and RV function when switched to a bosentan/riociguat combination for off-label use (559). There are no other reports or human studies of the use of riociguat in the pediatric PH population.

Novel therapies

FK506—Germline mutations causing loss of BMPR2 function are present in >80% of HPAH and ~20% of IPAH patients (adult data), and the presence of BMPR2 mutations is associated with worse pulmonary vascular remodeling (147, 413, 591). In addition, patients with IPAH without a BMPR2 mutation or with PAH associated with other conditions have reduced expression of BMPR2 in pulmonary arteries (558). Low-dose FK506 (tacrolimus) has been identified as a potent activator of BMPR2 and was shown to reverse pulmonary arterial occlusive changes in animal models. In PAECs isolated from patients with IPAH, low-dose tacrolimus reversed dysfunctional BMPR2 signaling (558). A randomized, placebo-controlled trial of tacrolimus showed improvements in WHO-FC, hemodynamics, and increased BMPR2 expression in peripheral mononuclear cells (557). The improvements noted in this trial were not significant and were only observed in a subset of patients with PAH (558).

Fasudil—Rho-kinase (ROCK) activity has been associated with several animal models of PAH and was found to be increased in expression in lung and pulmonary arteries from patients with severe PH (153, 532). Fasudil is an intravenous ROCK inhibitor that competes with ATP for the ATP-binding site on ROCK, thereby blocking ROCK activity and myosin light chain phosphorylation, which leads to ultimate vasodilation (268, 512). It has been studied in China and Japan for the treatment of PAH, PAH-CHD as well as PAH due to left ventricular dysfunction in adult patients and has been shown to improve hemodynamics (189, 279, 513, 654). There have been no studies of fasudil in the pediatric PH population.

Endothelial progenitor cells—Bone-marrow-derived endothelial progenitor cells (EPCs) have been shown to regenerate pulmonary vascular endothelium and reverse the changes of PAH in animal models (656). A recent meta-analysis concluded that stem cells are useful in the treatment of PAH in preclinical models and further human studies need to be performed (152). A small pilot study performed in China demonstrated that autologous EPCs transfused into children with PAH led to significant improvements in PVR, mPAP, 6MWD, and cardiac output with no adverse events (658). Intrapulmonary artery injection of stem cells has also been shown to improve persistent PAH after surgical correction of cardiac defects in three patients (21). Larger studies are needed to delineate the potential benefit of this therapy in patients refractory to established treatment protocols.

Surgical interventions

Pediatric PAH patients with supra-systemic PVR, multiple syncopal episodes, poor WHO-FC who are on maximal combined pharmacological therapy are candidates for surgical interventions either as a therapeutic intervention or as a palliative bridge to lung transplantation. The two procedures performed are balloon atrial septostomy (BAS) and reversed Potts shunt, both of which convert the physiology from that of PAH with supra-systemic PVR and increased RV afterload to the one in Eisenmenger's syndrome. Eisenmenger's syndrome is seen in longstanding left-to-right shunting lesions in congenital or acquired cardiac disease, where there is gradual development of PAH and ultimately the shunt reverses to a right-to-left one (521). The long-term outcomes for children with severe PAH are very poor with five-year survival rates ranging between 57% and 75%, with lung transplantation being the only option for severe PAH refractory to combined pharmacological treatment. In comparison, patients with Eisenmenger's syndrome have been reported to have superior long-term survival and transplant-free survival outcomes, and thus provided the concept of BAS and Potts shunt (151).

Atrial septostomy (AS)

AS is a percutaneous procedure by which an atrial communication is created via balloon dilation of the atrial septum and has been shown to improve symptoms and hemodynamics in patients refractory to vasodilator therapy (48, 337, 390). The atrial communication creates a right-to-left shunt to allow for decompression of the right heart with increased left ventricular preload and cardiac output with increased cyanosis, thus simulating Eisenmenger physiology (48). AS is considered either a palliative bridge to lung transplant in IPAH to increase survival while waiting for a donor organ or in patients with severe PH, WHO-FC III or IV and with recurrent syncope on combined medical therapy (235, 509). In resource-poor countries with limited access to PH drugs, it might be considered a therapeutic intervention but the long-term benefit of AS in the absence of an end-goal of lung transplant is unclear and should be weighed against the significant risks the procedure poses in pediatric patients with severe PAH. Data for outcomes of BAS mainly come from retrospective single-center studies with no randomized trials performed. One US center reported lung-transplantation free and repeat BAS-free survival at 30 days, 1 year, and 5 years to be 87%, 61%, and 32%, respectively (116). This data included both pediatric and adult patients (1-56 years) with a median age of 23 years and did not find any difference in serum biomarkers or hemodynamic findings pre-BAS and at 1 year or later follow-up. This finding was different

from another group that reported improvements in hemodynamic parameters after BAS, but a majority of the patients in the second study were not on pharmacological PH treatment (522). Another US center reported their data on event-free survival at 1, 2, and 3 years of 84%, 77%, and 69%, respectively, with significant improvements in symptoms and hemodynamic parameters, in patients who survived beyond 30 days post intervention (337). One reason for such high survival rates from this study is because they did not include patients who died within the first 30 days, which was 22% of their initial cohort. The increased postprocedural mortality from BAS stems from the sudden severe right-to-left shunting, which might lead to life-threating hypoxemia and subsequent hypoxic pulmonary vasoconstriction and impaired cardiac output. The sizing of the defect in BAS is critical since too much right-to-left shunt at the atrial level could be immediately life threatening because of insufficient pulmonary blood flow as well as severe desaturation in the brain and in the coronary circulation, and too small of a shunt may require repeated procedures because of spontaneous closure of the defect (390). The current recommendations from the European PPVDN and the 6th WSPH Pediatric Task Force are to avoid BAS in the following group of patients: (i) mean right atrial pressure >20 mmHg, (ii) resting arterial oxygen saturation <90%, (iii) severe RV failure, and (iv) patients with impending death (235, 506).

Reversed Potts shunt

Reversed Potts shunt is like BAS in that it creates a right-to-left shunt pathway in patients with severe PH and thus converting them into Eisenmenger physiology. This is performed by a direct side-by-side anastomosis from the left pulmonary artery (LPA) to the descending aorta and was first described in the pediatric population by Blanc et al (59, 82). This helps to decrease the RV afterload and act as a palliative bridge to lung transplant in severe PH patients who are on maximal combined pharmacological therapy with poor WHO-FC class, similar to BAS. Data about effectiveness of the Potts shunt in improving pulmonary hemodynamics and transplant-free survival are limited and mostly from case series. In one series of pediatric PAH patients who underwent elective Potts shunt placement, 8 out of 12 patients survived for a median of 27 months post shunt with significant improvements in pulmonary hemodynamics and WHO-FC at follow-up (12). Another similar small series with a median age of 13.5 months at the time of shunt placement were followed for a median of 17 months post shunt. Among those who survived the initial period after the shunt, there was improvement in their WHO-FC as well as the clinical symptomatology of RV failure (219). The largest case series of pediatric PH patients who received a Potts shunt included 24 patients with a median age of 7.7 years. They all had drug-refractory PAH with supra-systemic PVR, except for one patient who was operated on due to multiple central-line associated infections while on intravenous epoprostenol. After a median follow-up of 2.1 years, this cohort showed significant improvements in their WHO-FC, 6MWD, serum BNP/NT-proBNP levels, syncopal events, and ability to wean pulmonary vasodilator therapy. One child in this series progressed to lung transplantation (59). There have also been reports on transcatheter creation of Potts shunt by stenting the patent ductus arteriosus (PDA) in pediatric IPAH patients, with similar outcomes as the surgical procedure (87, 88, 163). The major benefit of the Potts shunt over BAS is that the right-to-left shunt is created after the coronary and cerebral circulation are supplied by the oxygenated left ventricular

output, thus avoiding myocardial and cerebral ischemia, with only the lower part of the body being cyanotic. The other benefit is that this directly offloads the RV both in systole and diastole, hence shifting the interventricular septum toward the RV and improving LV filling and cardiac output (12, 59, 163). This data is mostly anecdotal and has been challenged in the recent times using the CircAdapt model, which showed that the Potts shunt successfully transferred the supra-systemic PAH to an Eisenmenger physiology, but failed to decompress and offload the RV (146). There are no clinical trials comparing BAS to Potts shunt, and whether one is superior over the other is still unknown. Centers with higher volume and experience performing the Potts shunt and with extracorporeal life support backup for handling severe postoperative hypoxemia and low cardiac output states have better outcomes, especially as the initial postoperative period is associated with higher mortality.

Treatment Goals and Prognostic Tools for Monitoring and Follow Up

The identification of treatment goals is important as the US-FDA requires inclusion of a clinical endpoint for determining treatment efficacy of any drug or combination therapy. Important goals include death, transplantation and hospitalization, and the quality of the child's life. Other goals like weight gain, serum biomarkers, echocardiographic signs, invasive hemodynamics, CMRI, and exercise testing can also be studied. Exercise tests and 6MWTs are difficult to perform in the pediatric population, and invasive hemodynamic data from cardiac catheterization solely for the purpose of follow-up are not pursued due to the risks associated with the procedure in the pediatric population (62). A small cohort study of pediatric IPAH/HPAH and PAH-CHD patients found pulmonary stroke volume, mean systemic arterial pressure, and heart rate were the strongest predictors of survival (158). Observational studies have shown that echocardiographic parameters correlate with meaningful outcomes in the pediatric PH population. Right and left ventricular dimensions, TAPSE, and right-to-left ventricular dimension ratios correlate with WHO-FC, hemodynamics, and survival (476). A meta-analysis in 2015 reported that WHO-FC, NT-proBNP, mean RA pressure, PVRi, cardiac index, and AVT have been consistently reported as prognostic factors for outcomes in pediatric PH (477). Composite clinical worsening has been used as an endpoint for adult PAH and was recently studied in a Dutch national cohort as well as by the TOPP registry. Two-year outcomes from the REVEAL registry showed that the soft clinical worsening endpoints were highly predictive of subsequent mortality (474). The Dutch cohort reported occurrences of hospitalization, initiation of intravenous prostanoids, or functional deterioration (defined as WHO-FC deterioration, >15% decrease in 6MWD or both) were individually predictive of death or lung transplantation, and a composite outcome of the three components was suggested as an endpoint for further study (474). Another Dutch cohort study for pediatric PAH reported WHO-FC, TAPSE, and NT-proBNP were predictors of transplant-free survival, and improvements in these variables were associated with improved survival. The TOPP registry investigators reported composite clinical worsening (cCW) outcomes comprising PAH-related hospitalization, atrial septostomy, WHO-FC deterioration, intravenous/subcutaneous prostanoid initiation, syncope and occurrence/worsening of ≥PAH symptoms were associated with a higher risk of transplantation/death (62). They created three different cCW models, all of which were associated with an increased risk of death or lung transplant for all PAH subtypes combined.

However, when patients were separated based on etiology, for the PAH-CHD category none of the models or the individual components were associated with death and/or transplant.

Conclusion and Future Directions

In the last two decades, pediatric PH has been increasingly recognized as a separate entity with a different etiology and pathophysiology from adult PH. With the development of the Pediatric Task Force of the WSPH, TOPP registry, and PPH-Net, there has been increasing attention drawn to the pediatric-specific etiologies such as BPD-PH, PPHN, CDH-PH, and CHD-PAH. There are also an increasing number of off-label studies of drug regimens for pediatric PH. However, iNO is still the only drug approved by FDA for pediatric PH use. This is primarily due to the lack of randomized trials in the pediatric population and a lack of long-term safety data. The future goals of pediatric PH research should be focused on novel therapies for conditions unique to this age group and the conduct of well-designed, multicenter pediatric clinical trials of the drugs already being used in the adult patients. Identifying and validating composite clinical outcomes that can be reproduced across centers and different ages is key to developing clinical trials for monitoring treatment outcomes and defining goals and endpoints.

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Didactic Synopsis

Major Teaching Points

- Pulmonary hypertension (PH) is often a hidden component, occurring by itself or in association with lung diseases, and requires echocardiography and/or cardiac catheterization for diagnosis.
- Epidemiology and classification of pediatric pulmonary hypertension (PPH) has changed over time. Premature birth and bronchopulmonary dysplasia (BPD) are emerging as important causes of PPH; the risk is influenced by both prenatal and postnatal factors that adversely affect pulmonary vascular development.
- Several developmental disorders of the lung contribute to pediatric PH and are unique to this age group. They include lung hypoplasia secondary to congenital diaphragmatic hernia and genetic conditions such as alveolar capillary dysplasia.
- Congenital heart disease (CHD) is a major contributor to PPH; its presentation and clinical course are highly variable based on the type of CHD.
- Understanding the molecular mechanisms and changes at cellular and structural level in PH is the key to developing future drug targets for PPH.
- Developing diagnostic and treatment algorithms specific to PPH will help in identifying and properly classifying this component of PH.
- Inhaled nitric oxide is the only approved drug for the treatment of neonatal PPHN, and bosentan is the only approved drug for the treatment of pediatric PAH in the United States. Other drugs that target nitric oxide-cyclic GMP pathway, endothelin receptors, and prostacyclin pathways are also effective in PPH and are currently being used off-label.
- Future direction of PPH research needs to focus on developing novel drugs, other approaches besides vasodilation and on designing randomized clinical trials specifically in the pediatric population.

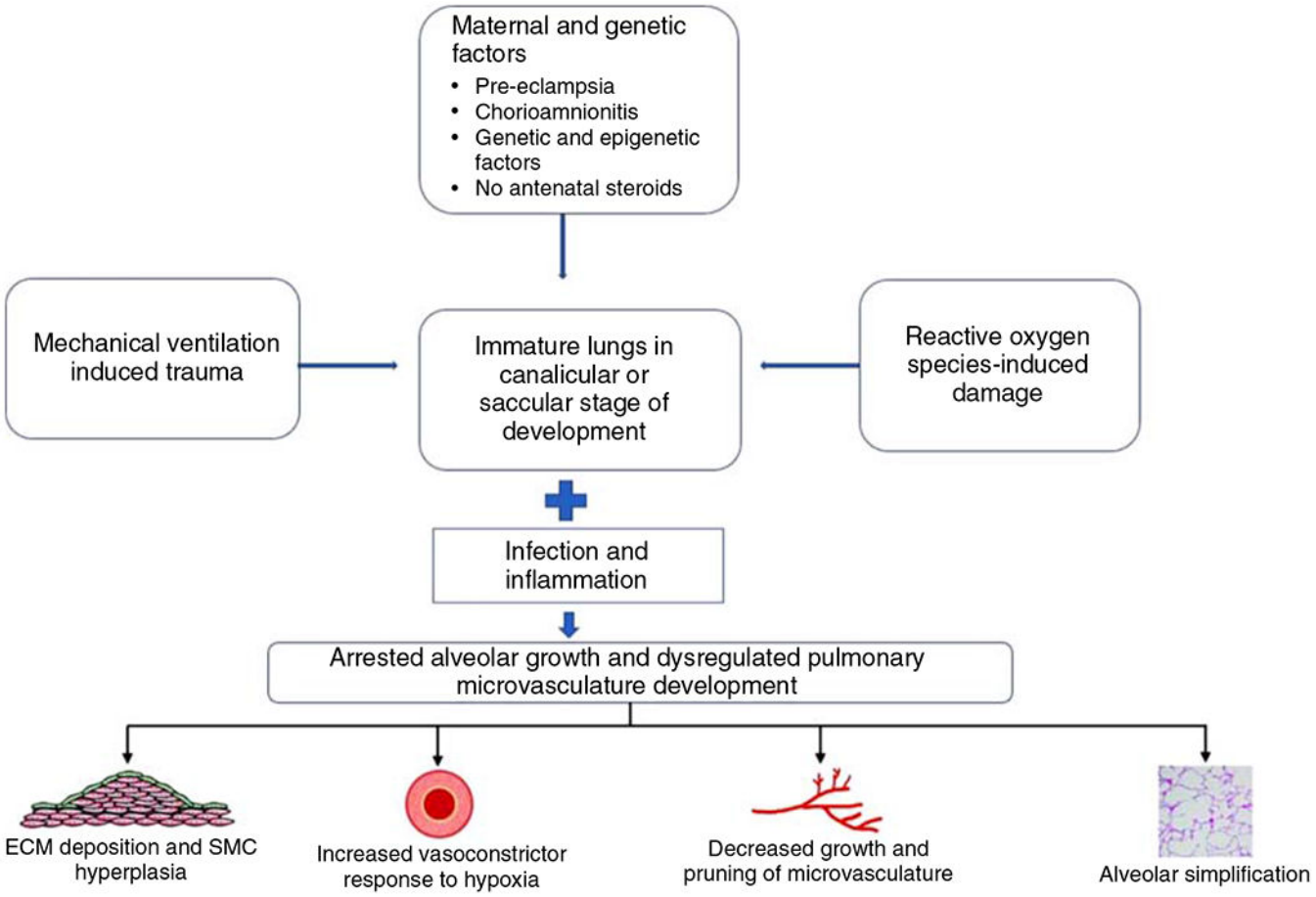

Figure 1.

Pathogenesis of bronchopulmonary dysplasia (BPD) associated pulmonary hypertension. The figure highlights the contribution of both prenatal and postnatal factors to the evolution of BPD. ECM, extracellular matrix; SMC, smooth muscle cell.

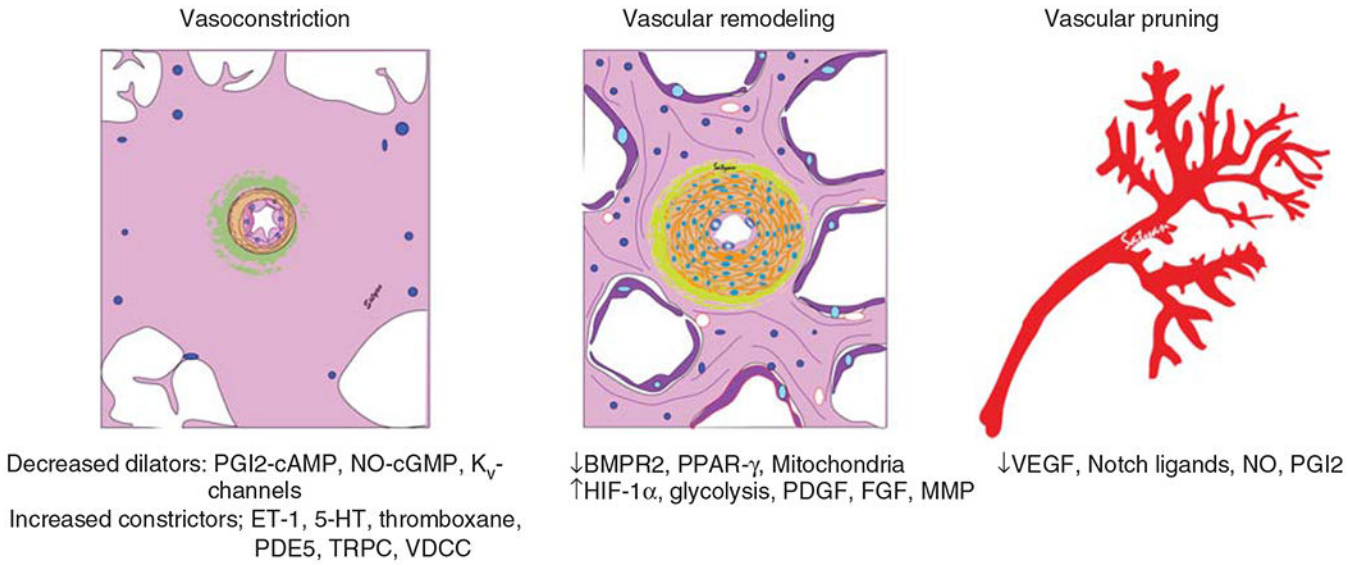

Figure 2.

Molecular and structural mechanisms of pulmonary vascular disease. PGI2, prostacyclin; NO, nitric oxide; sGC, soluble guanylate cyclase; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; PDE, phosphodiesterase; K_v channel, voltage-gated potassium channel; ET-1, endothelin-1; 5HT, 5-hydroxytryptamine; TRPC, transient receptor potential cation channel; VDCC, voltage-dependent calcium channel; BMPR2, bone morphogenetic protein receptor-2; PPAR-γ, peroxisome proliferator-activated receptor-γ; PDGF, platelet-derived growth factor; FGF, fibroblast growth factor; MMP, matrix metalloproteinase; HIF-1α, hypoxia inducible factor-1α VEGF, vascular endothelial growth factor.

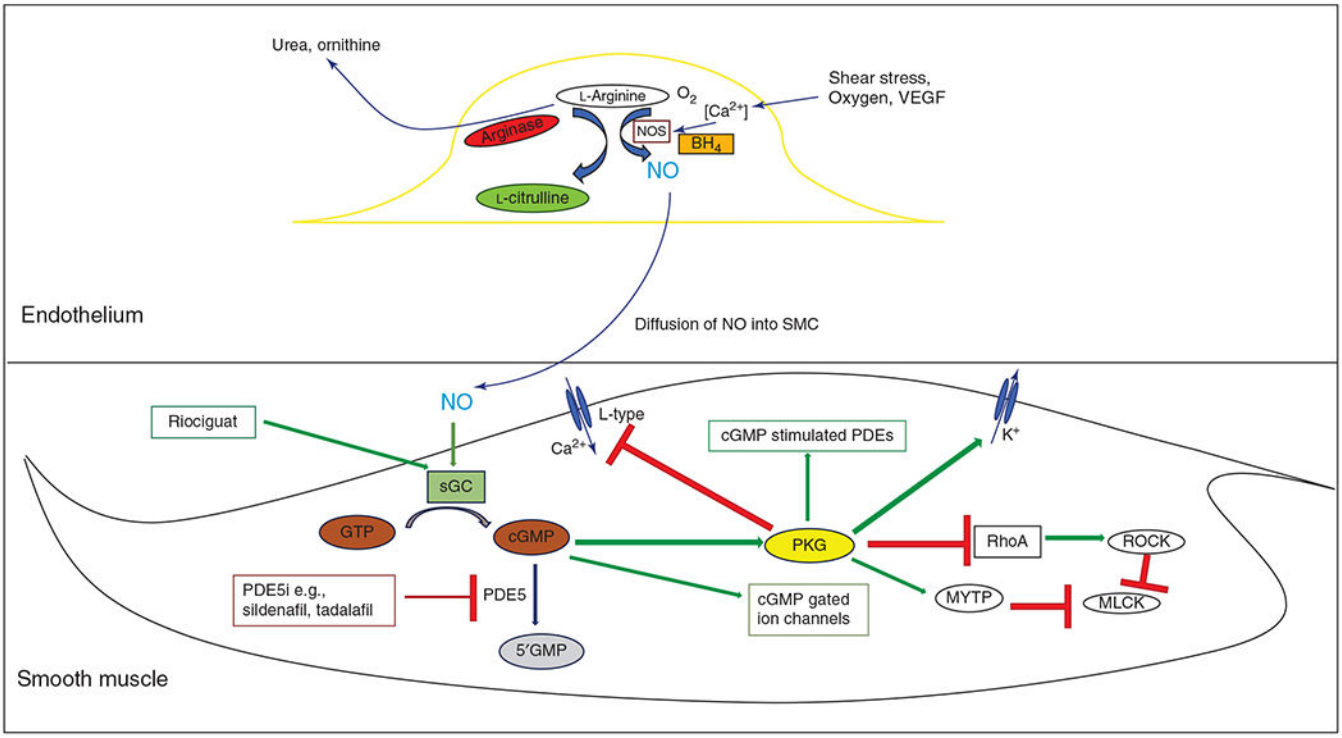

Figure 3.

NO-cGMP pathway showing paracrine effect of endothelial NO on vascular smooth muscle cell. NO, nitric oxide; NOS, nitric oxide synthase; BH4, tetrahydrobiopterin; sGC, soluble guanylate cyclase; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophsphate; PDE, phosphodiesterase; PDE5i, PDE5 inhibitor; PKG, protein kinase G; MYTP, myosin phsophatase targeting subunit; MLCK, myosin light chain kinase; ROCK, Rho kinase.

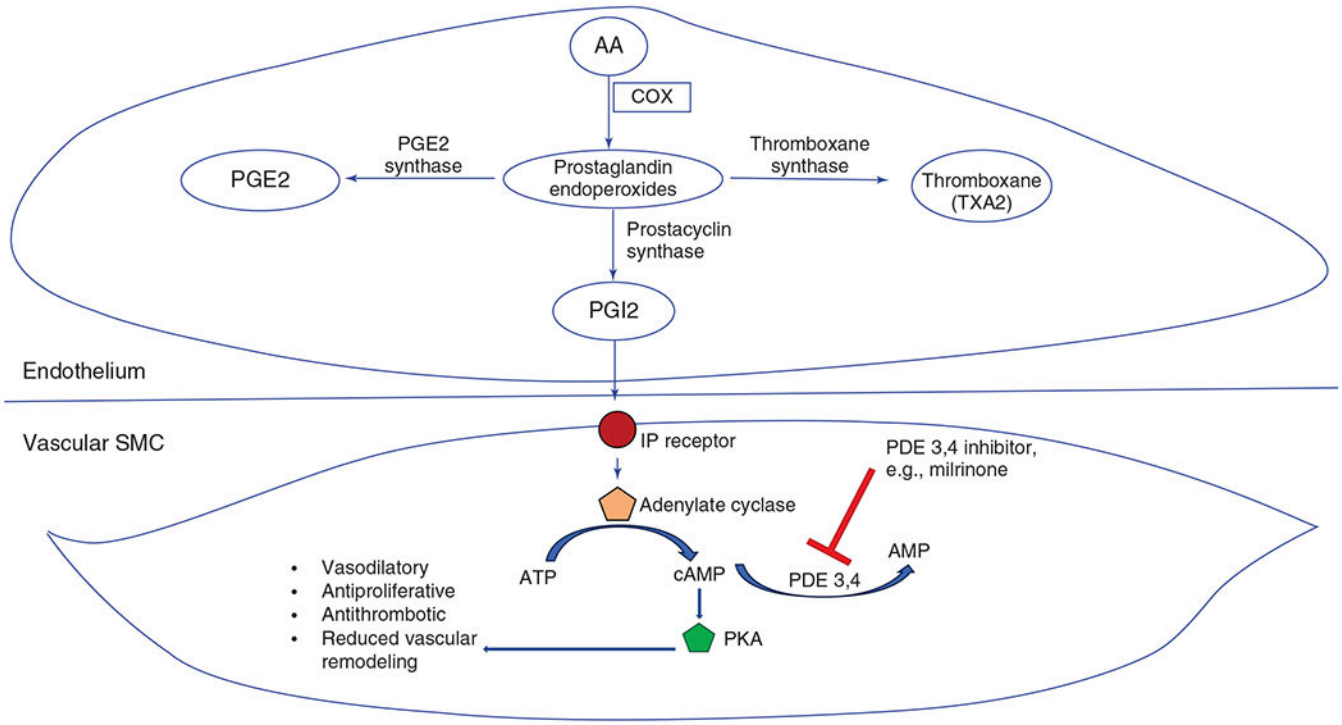

Figure 4.

Prostacyclin pathway role in pulmonary hypertension. AA, arachidonic acid; COX, cyclooxygenase; PGE2, prostaglandin E2; PGI2, prostacyclin; IP, inositol phosphate; PDE, phosphodiesterase; ATP, adenosine triphosphate; AMP, adenosine monophosphate; cAMP, cyclic AMP; SMC, smooth muscle cell; PKA, protein kinase A.

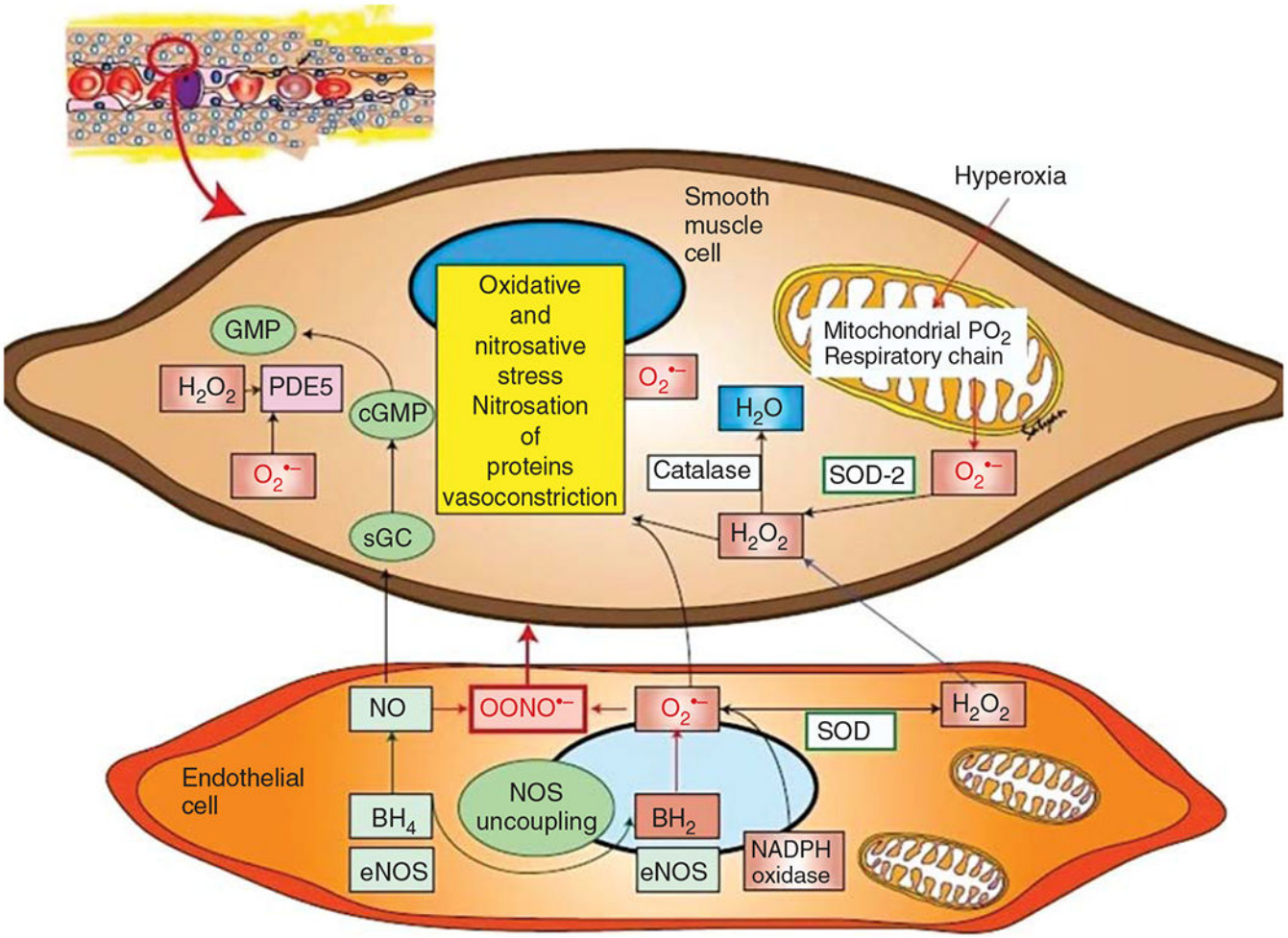

Figure 5.

Role of reactive oxygen species in pulmonary hypertension. $O_2^{\bullet-}$, superoxide anion; H_2O_2, hydrogen peroxide; PDE5, phosphodiesterase-5; GMP, guanosine monophosphate; cGMP, cyclic GMP; GTP, guanosine triphosphate; H_2O, water; NO, nitric oxide; $OONO^{\bullet-}$, peroxynitrite; SOD, superoxide dismutase; BH_4, tetrahydrobiopterin; BH_2, dihydrobiopterin; NOS, nitric oxide synthase; eNOS, endothelial NOS; NADPH, nicotinamide adenine dinucleotide phosphate dehydrogenase. Reused, with permission, from Apitz C, et al., 2016 (25); Reused, with permission, from Dennis KE, et al., 2009 (148); Reused, with permission, from Fike CD, et al., 2008 (181); Reused, with permission, from Irodova NL, et al., 2002 (267); Reused, with permission, from Wedgwood S and Black SM, 2003 (620).

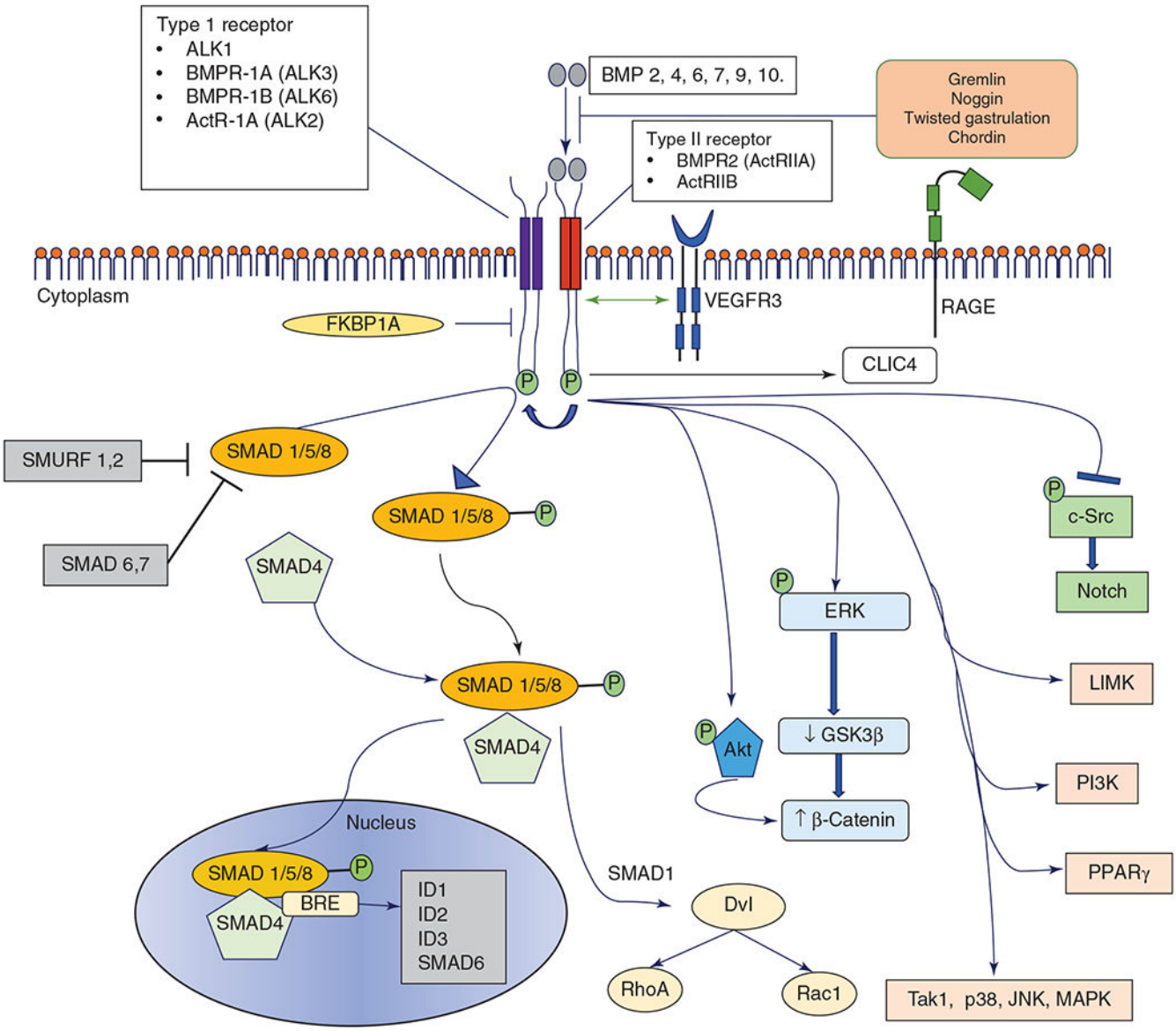

Figure 6.

A schematic representation of the BMPR2 signaling pathway. ActR, activin Receptor; Akt, protein kinase b; ALK, activin-like receptor; BMP, bone morphogenetic protein; BMPR, bone morphogenetic protein receptor; BRE, BMP response element; c-Src, proto-oncogene tyrosine-protein kinase Src; CLIC4, chloride intracellular channel 4; Dvl, disheveled; Erk, extracellular signal-regulated kinase; FKBP1A, FK binding protein 1A; GSK3-β, glycogen synthase kinase 3-β; ID, inhibitor of differentiation; JNK, c-Jun N-terminal kinase; LIMK, Lin11, Isl-1, and Mec-3 domain kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; PPARγ, peroxisome proliferator-activated receptor gamma; Rac1, Ras-related C3 botulinum toxin substrate 1; RAGE, receptor for advanced glycation end products; RhoA, Ras homolog gene family, member A; SMAD, mothers against decapentaplegic; SMURF, SMAD-specific E3 ubiquitin protein ligase; Tak1, transforming

growth factor-β activated kinase 1; VEGFR3, vascular endothelial growth factor receptor 3. Modified, with permission, from Andruska, A et al., 2018 (23). Licensed under CC-BY-4.0.

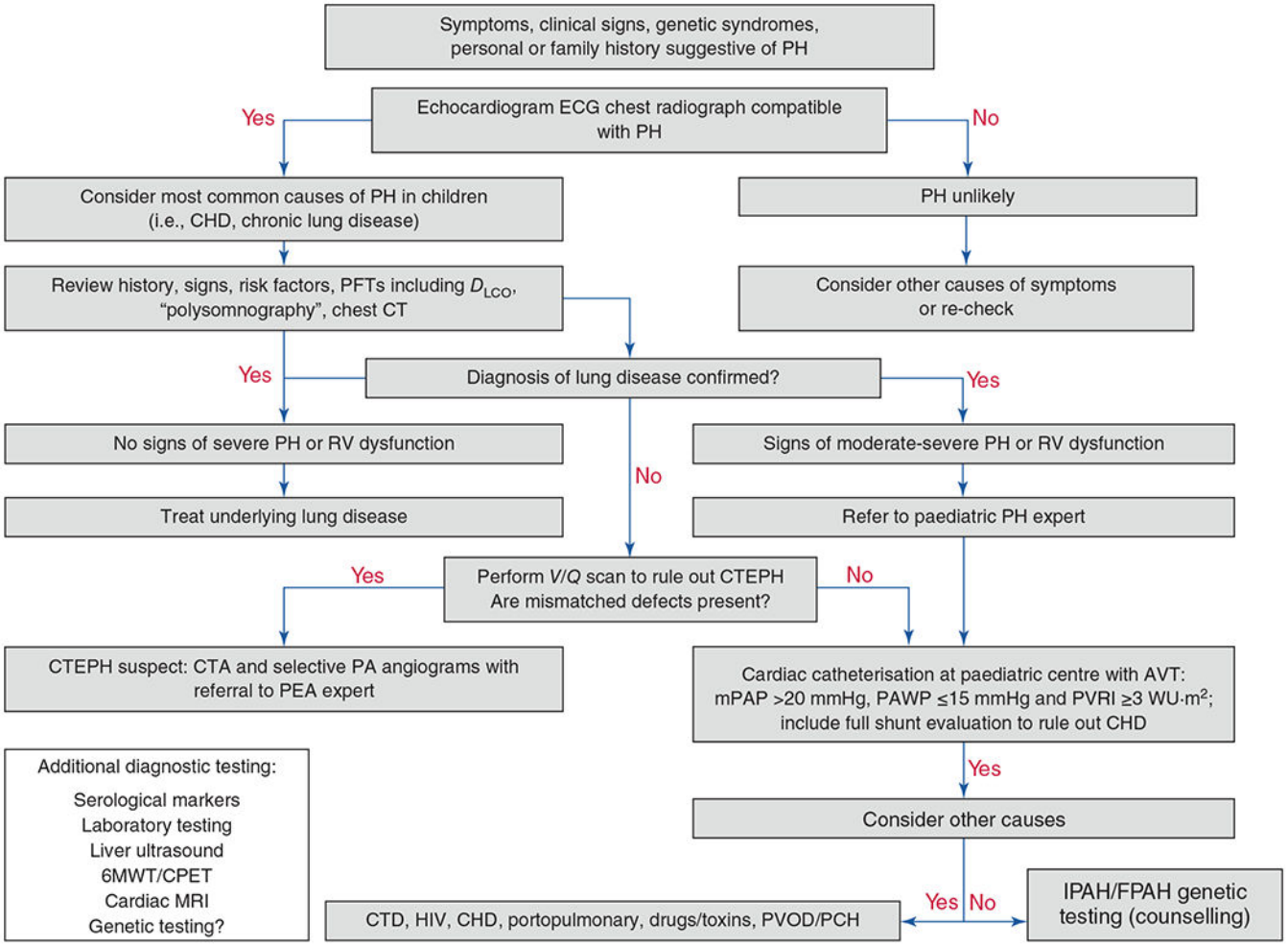

Figure 7.

Diagnostic algorithm for a child or young adult with suspected pulmonary hypertension. PH, pulmonary hypertension; ECG, electrocardiogram; CHD, congenital heart disease; PFT, pulmonary function test; CT, computed tomography; D_{LCO}, diffusing capacity for carbon monoxide; RV, right ventricle; CTEPH, chronic thromboembolic pulmonary hypertension; CTA, CT angiogram; PA, pulmonary artery; PEA, pulmonary endarterectomy; AVT, acute vasoreactivity testing; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVRI, pulmonary vascular resistance index; WU, Wood units; 6MWT, 6-minute walk test; MRI, magnetic resonance imaging; CPET, cardiopulmonary exercise testing; CTD, connective tissue disease; HIV, human immunodeficiency virus; PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary hemangiomatosis; IPAH, idiopathic pulmonary arterial hypertension; FPAH, familial pulmonary arterial hypertension. Adapted, with permission, from Rosenzweig EB, et al., 2019 (506). © 2019, The European Respiratory Society.

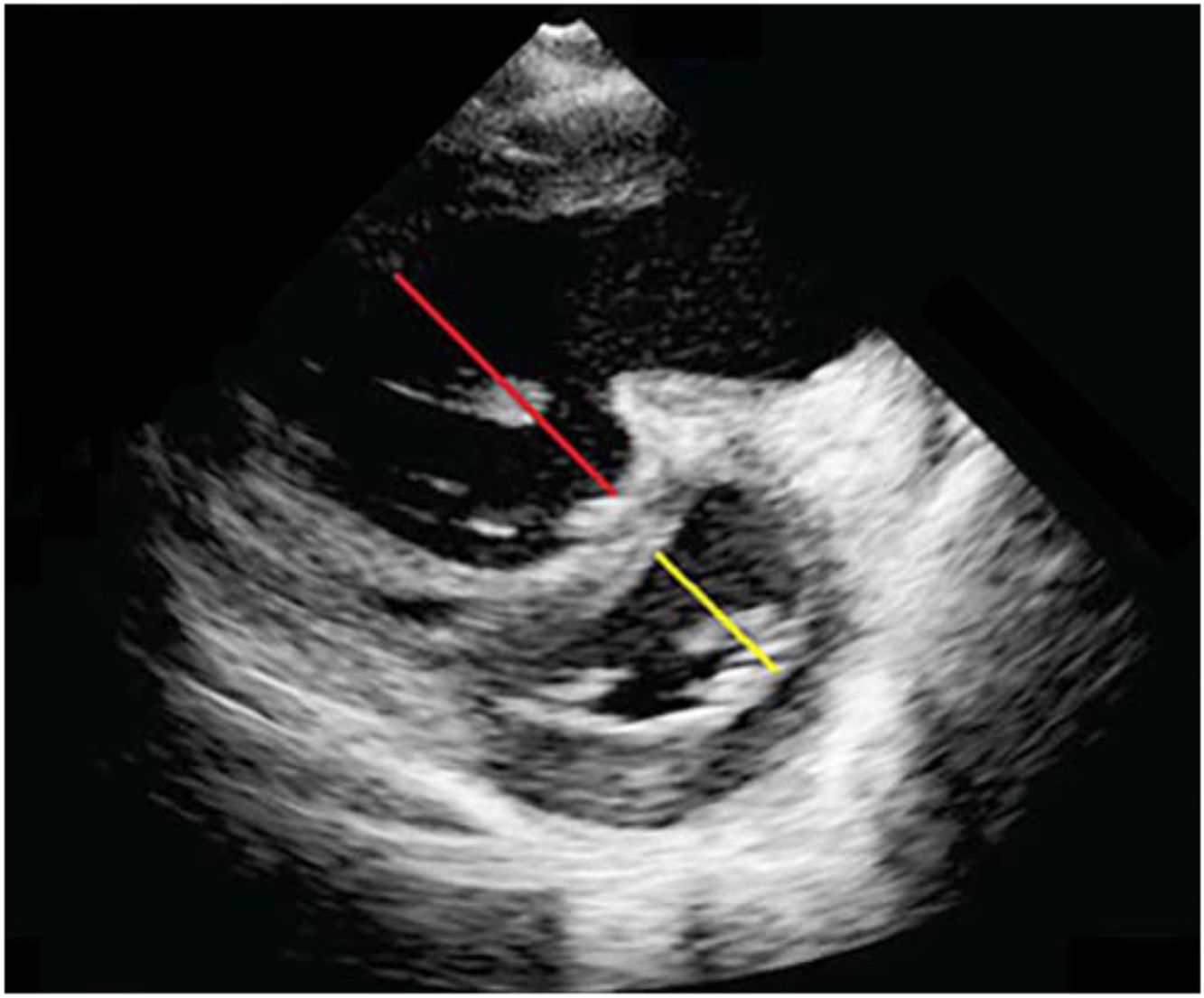

Figure 8.

Two-dimensional echocardiogram of a patient with severe PAH in the parasternal short-axis view showing D-shaped left ventricle (yellow line) and severe right ventricular dilatation (red line), along with biventricular remodelling.

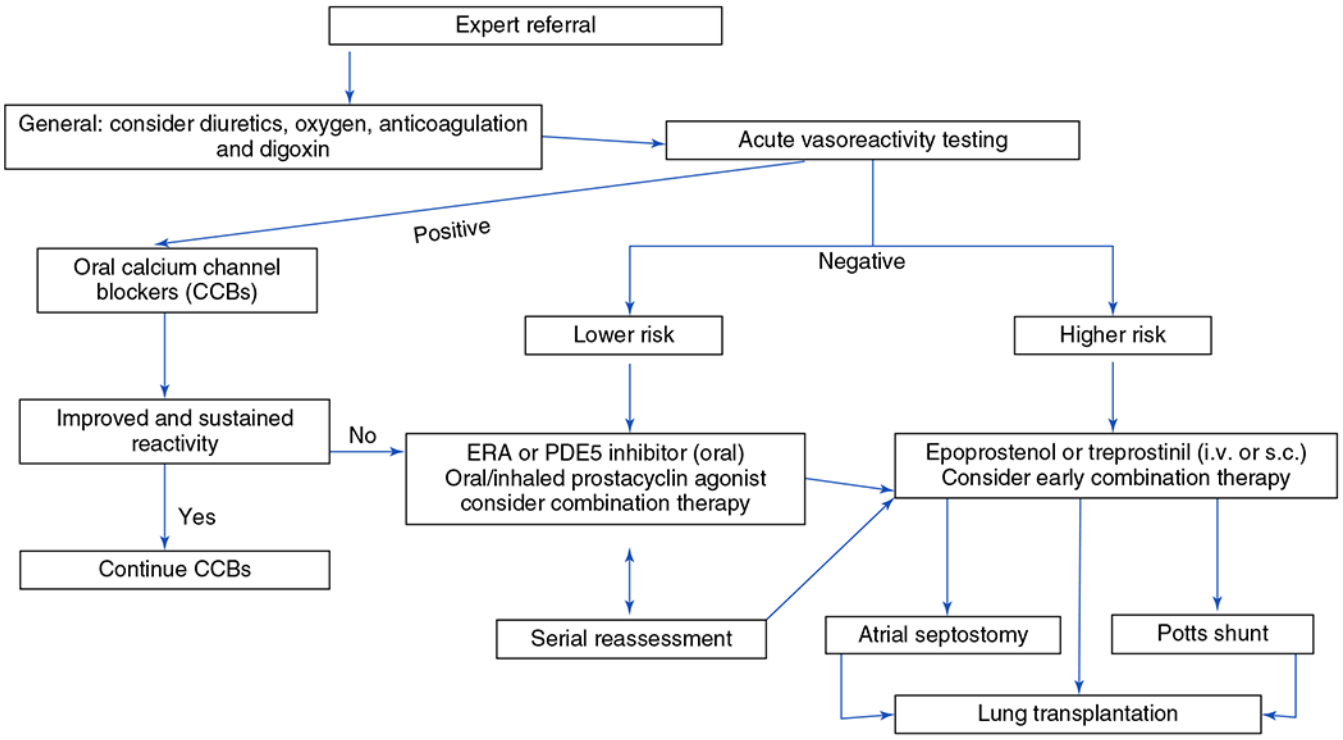

Figure 9.

Treatment algorithm for pediatric IPAH/HPAH as recommended by the 6th WSPH Pediatric Task Force. ERA, endothelin receptor antagonist; PDE5, phosphodiesterase 5; i.v., intravenous; s.c, subcutaneous. Adapted, with permission, from Rosenzweig EB, et al., 2019 (506). © 2019, The European Respiratory Society.

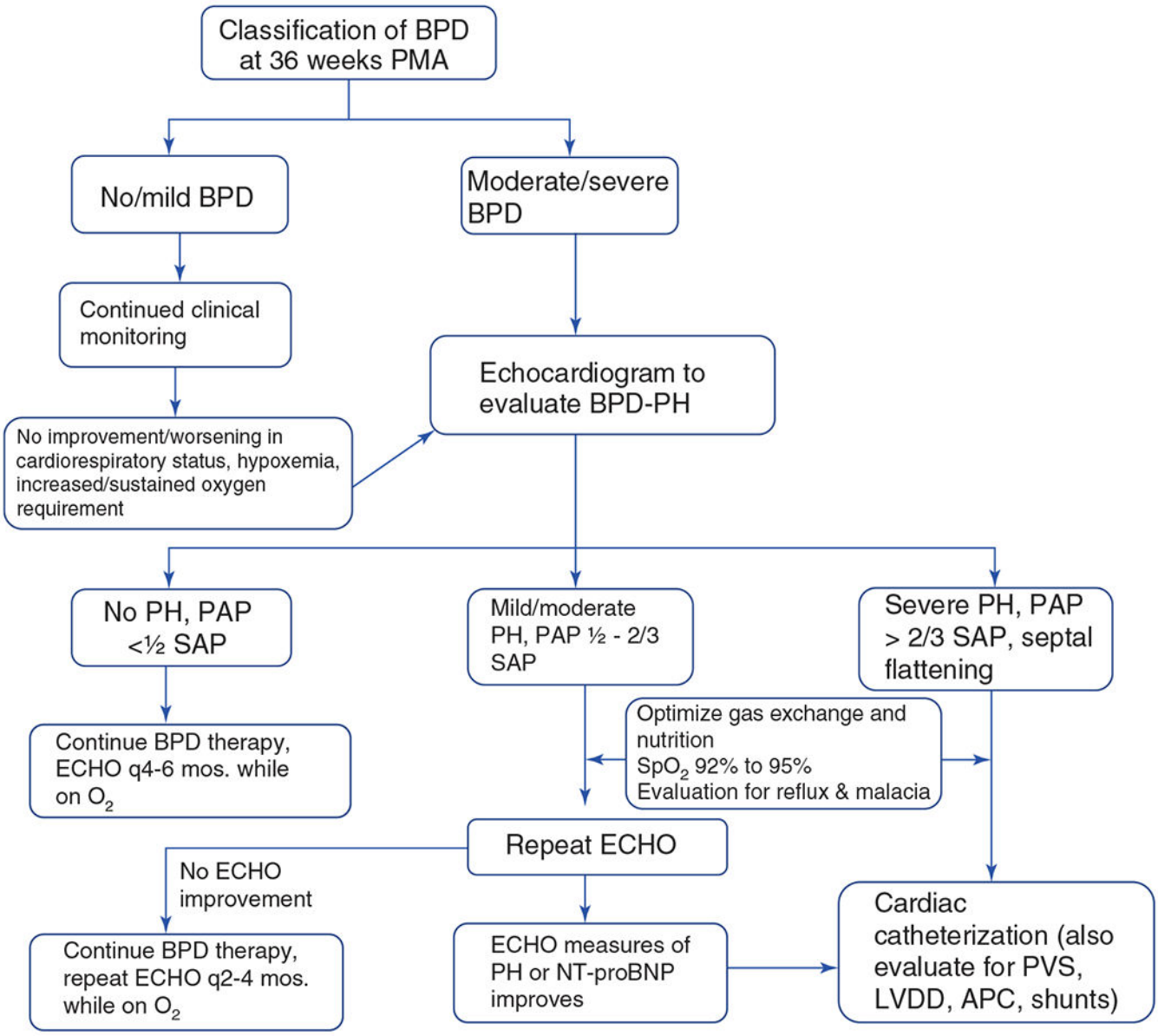

Figure 10.

Algorithm for the diagnosis and treatment of pulmonary hypertension in infants with bronchopulmonary dysplasia based on recommendations from PPHNet. PPHNet, pediatric pulmonary hypertension network; BPD, bronchopulmonary dysplasia; PH, pulmonary hypertension; ECHO, echocardiogram; PAP, pulmonary arterial pressure; SAP, systemic arterial pressure; BNP, brain-type natriuretic peptide; NT-proBNP, N-terminal proBNP; PVS, pulmonary vein stenosis; LVDD, left ventricular diastolic dysfunction; APC, aortopulmonary collateral. Modified, with permission, from Krishnan U, et al., 2017 (320).

Table 1

Definition of Pulmonary Hypertension Adapted from the European Pediatric Pulmonary Vascular Disease Network (EPPVDN) modeled on the 6th WSPH definitions (233–235)

1. Pulmonary hypertension
   a. mPAP > 20 mmHg in children > 3 months at sea level
2. Precapillary PH (e.g., pulmonary arterial hypertension)
   a. mPAP > 20 mmHg
   b. PAWP or LVEDP < 15 mmHg
   c. PVRI ≥ 3 Wu×m^2
   d. Diastolic TPG ≥ 7 mmHg
3. Isolated postcapillary PH in adults (predominantly LV diastolic dysfunction)
   a. mPAP > 20 mmHg
   b. PAWP or LVEDP > 15 mmHg
   c. PVRI < 3 Wu×m^2
   d. Diastolic TPG < 7 mmHg
4. Combination of precapillary and postcapillary PH in adults
   a. mPAP > 20 mmHg
   b. PAWP or LVEDP > 15 mmHg
   c. PVRI ≥ 3 Wu×m^2
5. Pulmonary arterial hypertension
   a. mPAP > 20 mmHg
   b. PAWP or LVEDP ≤ 15 mmHg
   c. PVRI ≥ 3 Wu×m^2 plus criteria for Group 1 PH
6. Idiopathic PAH (IPAH)–PAH with no underlying disease known to be associated with PAH
7. Heritable PAH (HPAH)–PAH with no known underlying disease but with positive family history or positive genetic testing of the index patient
8. Eisenmenger syndrome–Patient with longstanding pulmonary hypertension, supra-systemic PVR and PAP, and accordingly, right-to-left cardiovascular shunting with systemic hypoxemia (e.g., unrepaired VSD or PDA)
9. Pulmonary hypertensive vascular disease For biventricular circulations: mPAP > 20 mmHg and PVR index ≥ 3 WU×m^2 For circulations with cavopulmonary anastomosis (e.g., Fontan physiology): Mean TPG > 6 mmHg (calculate mPAP minus mLAP or PAWP) or PVR index > 3 WU×m^2

PH, pulmonary hypertension; mPAP, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; LVEDP, left ventricular end-diastolic pressure; PVRI, pulmonary vascular resistance index; TPG, transpulmonary gradient; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; VSD, ventricular septal defect; PDA, patent ductus arteriosus; WU, Wood units mLAP, mean left atrial pressure.

Adapted, with permission, from Rosenzweig EB, et al., 2019 (506).

Table 2

Revised Clinical Classification of Pediatric Pulmonary Hypertension as Proposed by 2018 World Symposium on Pulmonary Hypertension, Nice, France. Pediatric Task Force

Group 1. Pulmonary arterial hypertension (PAH)	1.1 Idiopathic PAH (IPAH) 1.2. Heritable PAH (HPAH) 1.3. Drug and toxin related PAH 1.4. Associated PAH	
		1.4.1. PAH associated with CTD 1.4.2. PAH associated with HIV infection 1.4.3. PAH associated with portal hypertension 1.4.4. Congenital heart disease 1.4.5. Schistosomiasis
	1.5. PAH long-term responders to CCBs 1.6. PAH with overt features of venous/capillaries (PVOD/PCH) involvement 1.7. Persistent PH of the newborn (PPHN) syndrome	
Group 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 cardiomyopathy–pulmonary vein stenosis (isolated or associated with BPD), cor triatriatum, obstructed Total Anomalous Pulmonary Venous Return (TAPVR), Mitral/aortic stenosis (including supra/subvalvular) and coarctation of aorta	
Group 3. PH due to lung disease 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 syndromes 3.6. Long-term exposure to high altitudes 3.7. Developmental lung diseases	
		Bronchopulmonary dysplasia Congenital Diaphragmatic Hernia Down syndrome Alveolar capillary dysplasia with “misalignment of veins” (FOXF1) Lung hypoplasia, acinar dysplasia Surfactant deficiency TTF-1/NKX2-1 TBX4 Pulmonary interstitial glycogenesis Pulmonary alveolar proteinosis Pulmonary lymphangiectasia
Group 4. PH due to pulmonary artery obstructions	4.1. Chronic thromboembolic PAH 4.2. Pulmonary artery obstructions either congenital or acquired after cardiac surgery	
Group 5. PH due to unclear/ multifactorial mechanisms	5.1. Hematological 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	

	5.4. Others: tumor obstruction, fibrosing mediastinitis, chronic renal failure, complex CHD–unoperated or operated single ventricle, pulmonary atresia with ventricular septal defect and major aorto-pulmonary collaterals, hemitruncus, absent pulmonary artery and isolated pulmonary artery of ductal origin

CTD, connective tissue disease; HIV, human immunodeficiency virus; CCB, calcium channel blocker; PVOD, pulmonary venous obstructive disease; PCH, pulmonary capillary hemangiomatosis; LV, left ventricle; BPD, bronchopulmonary dysplasia; CHD, congenital heart disease.

Adapted, with permission, from Rosenzweig EB, et al., 2019 (506).

Table 3

Clinical and Hemodynamic Characteristics of Major Etiologies of Pediatric Pulmonary Hypertension

	Population/risk factors/clinical features	Echocardiography findings	Treatment and prognosis
Idiopathic and hereditary PAH (IPAH/HPAH)	IPAH – PAH with no disease known to be assocated with it HPAH – Familial history of PAH or known genetic mutation associated with PAH	mPAP > 20 mmHg, PAWP or LVEDP ≤ 15 mmHg, PVRI ≥ 3Wu×m^2	Pulmonary vasodilator therapy
PAH-CHD	ASD, VSD, PDA, AV canal defects, TGA, Eisenmenger's syndrome, single ventricle physiology	Elevated PVRI in addition to presence of shunt lesions with affect pulmonary and systemic flow	Catheterization to perform AVT and assess for operablity, selective pulmonary vasodilators, surgical repair
BPD-PH	Prematurity, low birthweight, growth restriction, mechanical ventilation	Elevated PVR and TRJV, flattened IVS, RV hypertrophy, suspicion for PVS should trigger CTA or cardiac catheterization	Oxygen, ventilatory management, selective pulmonary vasodilators
PPHN	Neonatal population, meconium aspiration, maternal SSRIs, pneumonia, RDS, CDH, pulmonary hypoplasia, renal dysplasias	Suprasystemic PA and RV pressures after birth	Oxygen, acid-base balance, surfactant, mechanical ventilation, iNO, milrinone, inhaled and subcutaneous prostaglandins. ECMO in medically refractory PPHN
PH from CDH	Neonates and infants with CDH	Elevated PVR and mPAP, along with possible presence of LV dysfunction	Pulmonary selective vasodilators
PH from left heart disease	Older children with CHD, history of repair of coarctation of aorta, VSD repair, heart transplant, HLHS and its variants, cardiomyopathies, LV systolic or diastolic dysfunction	mPAP > 20 mmHg, PAWP or LVEDP > 15 mmHg, PVRI < 3 Wu×m^2	Treatment of left heart disease, surgical repair in children with CHD after assesing operability

PH, pulmonary hypertension; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; PAH, pulmonary arterial hypertension; CHD, congenital heart disease; ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosis; HLHS, hypoplastic left heart syndrome; CDH, congenital diaphragmatic hernia; SSRI, selective serotonin reuptake inhbitor; AV, atrioventricular; TGA, transposition of great arteries; BPD, bronchopulmonary dysplasia; PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome, iNO, inhaled nitric oxide; ECMO, extracorporeal membrane oxygenation, PAWP, pulmonary arterial wedge pressure; LVEDP, left ventricular end-diastolic pressure; PVRI, pulmonary vascular resistance index; mPAP, mean pulmonary artery pressure; TRJV, tricuspid regurgitant jet velocity; IVS, interventricular septum; PVS, pulmonary vein stenosis; CTA, computed tomography with angiography.

Table 4

Comparison Between Precapillary, Postcapillary and Mixed PH

	Precapillary PH	Postcapillary PH	Mixed pre- and postcapillary PH
Etiologies	Group 1 and 3 PH predominantly	Group 2 PH (left heart disease including systolic and diastolic LV dysfunction), PVS	Predominantly left heart disease progressing to increased PVR due to pulmonary vascular remodeling over time
Hemodynamic findings and diagnosis	mPAP > 20 mmHg, PAWP or LVEDP ≤ 15 mmHg, PVRI > 3 Wu×m^2, Diastolic TPG ≥ 7 mmHg	mPAP > 20 mmHg, PAWP or LVEDP > 15 mmHg, PVRI < 3 Wu×m^2, Diastolic TPG < 7 mmHg	mPAP > 20 mmHg, PAWP or LVEDP > 15 mmHg, PVRI ≥ 3 Wu×m^2, Diastolic TPG ≥ 7 mmHg
Treatment	Targeted toward conventional PH therapy	Targeted toward treating left heart dysfunction	Combination of both approaches of treating pre- and postcapillary PH

PH, pulmonary hypertension; LV, left ventricle; PVR, pulmonary vascular resistance; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; LVEDP, left ventricular end-diastolic pressure; PVRI, pulmonary vascular resistance index; TPG, transpulmonary gradient (31,426, 427).

Table 5

Panama Classification for Pediatric Pulmonary Vascular Disease as Proposed by the Pulmonary Vascular Research Institute (PVRI) Pediatric Task Force in 2011

Category	Description
1	Prenatal 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

Modified, with permission, Cerro MJ, et al., 2011 (106).

Table 6

Panama Functional Classification for Pediatric PH as Proposed by Pulmonary Vascular Research Institute (PVRI) Pediatric Task Force, 2011

	0 to 0.5 year	0.5 to 1 year	1 to 2 years	2 to 5 years	5 to 16 years
I	Asymptomatic, growing and developing normally, no limitation of physical activity (PA). Gains head control, increases body tone, rolls over, sits without support gradually	Asymptomatic, growing on centiles, no limitation of PA. Mobile, sitting, grasping, crawling, playing	Asymptomatic, growing on centiles, no limitation of PA. Standing, starting to walk, climbing	Asymptomatic, growing on centiles, no limitation of PA. Attending school normally and playing sports with classmates	Asymptomatic, growing on centiles, no limitation of PA. Attending school normally and playing sports with classmates
II	Slight limitation of PA, unduly dyspneic and fatigued, falling behind developmental milestones. Comfortable at rest and gaining weight	Slight limitation of PA, unduly dyspneic when playing. Delayed milestones but normal growth and comfortable at rest	Slight limitation of PA, unduly dyspneic when playing. Delayed milestones but normal growth and comfortable at rest	Slight limitation of PA, unduly dyspneic as compared to classmates. <75% attendance at school. Comfortable at rest and normal weight gain	Slight limitation of PA, unduly dyspneic as compared to classmates. <75% attendance at school. Comfortable at rest and normal weight gain
IIIa	Marked limitation of PA, unduly fatigued. Quiet, needs frequent naps, poor feeding, growth, and regression of learned milestones. Comfortable at rest	Marked limitation of PA, unduly fatigued while playing. Quiet, needs frequent naps, poor feeding, growth, and regression of learned milestones. Comfortable at rest	Marked limitation of PA, unduly fatigued while playing. Quiet, needs frequent naps, poor feeding, growth, and regression of learned milestones. Comfortable at rest	Marked limitation of PA, regression of milestones, not climbing stairs, reluctant to play with friends. Less than ordinary activity causes symptoms. <50% attendance at school	Marked limitation of PA, no attempt at sports. Less than ordinary activity causes symptoms. Comfortable at rest. <50% attendance at school
IIIb	IIIa plus severely compromised growth and feeding	IIIa plus severely compromised growth and feeding	IIIa plus severely compromised growth and feeding	Unable to attend school, mobile at home, needs wheelchair outside. Compromised growth, poor feeding plus IIIa	Unable to attend school, mobile at home, needs wheelchair outside. Compromised growth, poor feeding plus IIIa
IV	Unable to carry out any PA without severe symptoms and is not interacting with family. Right heart failure (RHF) plus syncope	Unable to carry out any PA without severe symptoms and is not interacting with family. RHF plus syncope	Unable to carry out any PA without severe symptoms and is not interacting with family. RHF plus syncope	Unable to carry out any physical activity without severe symptoms, unable to attend school, not interacting with friends, wheelchair dependent, RHF plus syncope	Unable to carry out any physical activity without severe symptoms, unable to attend school, not interacting with friends, wheelchair dependent, RHF plus syncope

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Table 7

Determinants of Risk in Pediatric Pulmonary Hypertension

Lower risk	Determinants of risk	Higher risk
No	Clinical evidence of RV failure	Yes
No	Progression of symptoms	Yes
No	Syncope	Yes
Normal height and BMI	Growth	Failure to thrive
I and II	WHO FC	III and IV
Minimally elevated for age or not elevated	Serum NT-proBNP	Greatly elevated for age > 1200 pg/mL (>1 year old) Rising NT-proBNP level
Minimal RA/RV enlargement	Echocardiography, CMRI	Severe RA/RV enlargement
No RV systolic dysfunction		RV systolic dysfunction
RV/LV e.s. ratio < 1		RV/LV e.s. ratio > 1.5
TAPSE normal (z > −2)		TAPSE abnormal (z < −3)
S/D ratio < 1 (TR jet)		S/D ratio > 1.4 (TR jet)
PAAT > 100 ms (> 1 year old)		PAAT < 70 ms (> 1 year old) Pericardial effusion
CI > 3.0L/min/m^2	Invasive hemodynamics	CI < 2.5 L/min/m^2
mRAP < 10 mmHg		mRAP > 15 mmHg
mPAP/mSAP < 0.5		mPAP/mSAP > 0.75
Acute vasoreactivity positive		PVRI > 15 Wu×m^2

BMI, body mass index; BNP, brain natriuretic peptide; CI, cardiac index; CMR, cardiovascular magnetic resonance imaging; e.s., end-systolic; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; mSAP, mean systemic artery pressure; NT-proBNP, N-terminal proBNP; PAAT, pulmonary artery acceleration time by transthoracic Doppler echocardiography; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PHVD, pulmonary hypertensive vascular disease; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; RA, right atrium; RV, right ventricle; S/D ratio, systolic/diastolic duration ratio by Doppler echocardiography; SVR, systemic vascular resistance; SVRi, systemic vascular resistance index; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; Vo2max, maximum rate of oxygen consumption; WHO, World Health Organization; WU, Wood units.

Table 8

Recommendations for Different Diagnostic Strategies for Pediatric PH

Diagnostic tool for PH	Recommendations for use at time of diagnosis of PH	Recommendations for use during follow-up
Chest X-ray	Recommended but not necessary to perform at baseline	No need at follow-up visits, unless there is clinical reason
NT-proBNP	Part of initial workup	Serial measurements important to follow up disease severity, progression and response to treatment
Transthoracic echocardiography	Necessary part; need to include mPAP, end-diastolic PAP, RV longitudinal systolic function, RV strain, RV size and function, RV base/apex ratio, RV systolic-to-diastolic duration ratio, tissue Doppler velocities, RVOT size enlargement, RA and RV size enlargement, RA function, end-systolic LV eccentricity index, end-systolic RV/LV diameter ratio and indicators of diastolic LV dysfunction	Should be performed every 3 to 6 months, sooner if there is clinical worsening
Cardiac catheterization	Indicated in all patients to confirm diagnosis, determine severity and anytime when PH-specific therapy considered; exceptions are PPHN and BPD-PH, weight <2 to 5 kg who might be unstable and in critically ill patients; need to include AVT, PVR/SVR ratio, PVRI, oximetry, pressure measurements of RA, RV, PA, LA, PA wedge and systemic artery, VO_2	Repeated at clinical discretion based on clinical worsening, failure to reach treatment goals with multidrug therapy, listing for heart or heart-lung transplant, and every 12 to 24 months in stable patients after full non-invasive evaluation has been performed
CT angiography	High-resolution chest CT with angiography at initial evaluation; evaluate MPA/AO ratio, lung parenchyma, PA pruning and pulmonary veins	Not recommended for repeat unless presence of PVS or before considering transplant
Cardiac MRI	Gold standard for evaluating RV size, mass, and function. Ventricular EDV, RVEF, and stroke volume predict morbidity and mortality in adults	Based on clinical discretion
Genetic testing	Recommended for all children diagnosed with IPAH/HPAH in addition to counseling and for first-degree family members of patients with PAH and a known mutation	Not indicated
Polysomnography	Recommended in patients diagosed with PH at risk for sleep-disordered breathing including trisomy 21, patients with small upper airways, daytime sleepiness	Not indicated unless abnormal during initial evaluation

PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; IPAH, idiopathic PAH; HPAH, hereditary PAH; CT, computed tomography; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-brain natriuretic peptide; RV, right ventricle; LV, left ventricle; RVOT, RV outflow tract; RA, right atrium; LA, left atrium; PA, pulmonary artery; mPAP, mean pulmonary arterial pressure; RVEF, RV ejection fraction; EDV, end diastolic volume; MPA, main PA; AO, aorta; BPD, bronchopulmonary dysplasia; PPHN, persistent pulmonary hypertension of the newborn; PVS, pulmonary vein stenosis.