Journal of Clinical & Experimental Cardiology

Gorenflo et al., J Clin Exp Cardiolog 2012, S:8
DOI: 10.4172/2155-9880.S8-011

Review Article Open Access

Neonatal and Childhood Pulmonary Hypertension - An Update (2012)

Matthias Gorenflo[1]*, Siegrun Mebus[2], Ian Adatia[3], Maria J del Cerro[4], Damien Bonnet[5] and Maurice Beghetti[6]

[1]*Department of Ped. Cardiol and Congenital Cardiology, University Med. Ctr., Heidelberg, Germany*
[2]*Department of Pediatric Cardiology and Congenital Heart Disease, Deutsches Herzzentrum München, Technische Universität München, Munich, Germany*
[3]*Department of Pediatrics, Div Pediatric Cardiology Pulmonary Hypertension Clinic, Stollery Children's Hospital, Mazankowski Heart Institute, University of Alberta, Edmonton, Alberta, Canada*
[4]*Pediatric Pulmonary Hypertension Unit, Pediatric Cardiology "La Paz" Hospital Madrid, Spain*
[5]*Pediatric Cardiology, University Paris Descartes, Hospital Necker, Paris, France*
[6]*Pediatric Cardiology Unit, Children's University Hospital, Geneva, Switzerland*

Abstract

Although substantial advances have been made in our understanding of pulmonary hypertensive vascular disease there remain important challenges to overcome in designing pediatric drug trials and improving long term survival. We address the current classifications and review the current knowledge on epidemiology, pathogenesis and therapy of pulmonary hypertension.

Abbreviations: 6MWT: 6-Min Walk Test; ACVRL1: Activin A Receptor Type II-Like Kinase-1; ANP: Atrial Natriuretic Peptide; APAH: Associated Pulmonary Arterial Hypertension; AVR: Acute Vasodilator Response; BMPR-II: Bone Morphogenetic Protein Type II Receptor; BNP: b-Type Natriuretic Peptide; CHD: Congenital Heart Disease; CXR: Chest X-Ray; ET-1: Endothelin-1; EPCs: Circulating Endothelial Progenitor Cells; HPAH: Heritable Pulmonary Arterial Hypertension; IPAH: Idiopathic Pulmonary Arterial Hypertension; MRI: Magnetic Resonance Imaging; PAH: Pulmonary Arterial Hypertension; PAH-CHD: Pulmonary Arterial Hypertension Associated with Congenital Heart Disease; PDE-5: Phosphodiesterase Type 5; PH: Pulmonary Hypertension; PHVD: Pulmonary Hypertensive Vascular Disease; PVR: Pulmonary Vascular Resistance; TAPSE: Tricuspid Annular Plane Systolic Excursion; TGF-β: Transforming Growth Factor – Beta; TIMPs: Endogenous Tissue Inhibitors of Matrix Metalloproteinases; TOPP: Tracking Outcome and Practice in Paediatric Pulmonary Hypertension

Introduction

Pulmonary Hypertension (PH) is a fatal disease affecting patients of all ages. In the last decade, substantial progress has been made in the understanding of the underlying pathobiology, which has been translated successfully into the development of medical treatments. This review aims to summarize our current knowledge with a special focus on pediatric pulmonary hypertension.

Definition and classification

The Dana Point classification of PH [1], (Table 1), categorizes very well the different etiologies of PH. It reflects the epidemiology of PH in adults and has been adopted by federal drug agencies to guide and monitor the use of pulmonary hypertensive specific therapy. It is an invaluable tool in the understanding of PH and facilitates drug trials in adults. PH is defined as a mean pulmonary artery pressure ≥ 25 mmHg [2]. For the pediatric population this definition raises some problems: 1) It is not applicable to neonates. 2) It does not address the large cohort of patients presenting with Congenital Heart Disease (CHD) where PH may be associated with unrestricted left-to-right shunt but normal pulmonary vascular resistance (< 3 Wood Units*m^2). 3) It fails to include an increasing number of patients who have undergone a cavo-pulmonary anastomosis who may have pulmonary vascular disease with a mean pulmonary artery pressure less than 25 mmHg.

These problems have been discussed at a conference held in Panama in 2011. According to the Panama Classification 2011, pediatric pulmonary hypertensive vascular disease is defined as a mean pulmonary artery pressure equal or > 25 mmHg and a pulmonary vascular resistance index > 3.0 Wood units * m^2 for biventricular circulations [3].

The Panama classification attempts to address Pulmonary Hypertensive Vascular Disease (PHVD) more broadly than the Dana Point Classification and is particularly cognizant of the heterogeneity of pediatric PH in comparison to adult onset PH. This acknowledges the increasing awareness that post cavo-pulmonary anastomosis, exercise limitation or cyanosis may be due to an increased pulmonary vascular resistance and that these patients might benefit from targeted therapies aimed at reducing the pulmonary vascular resistance even though the mean PA pressure < 25mmHg. [4-6]. Therefore, the Panama Classification includes a definition of PHVD of PVRI > 3.0 WUm^2 or a transpulmonary gradient > 6 mmHg for patients after cavo-pulmonary anastomosis.

The Panama classification divides pediatric PHVD into 10 categories (Table 2) ordered according to the estimated frequency of occurrence and currently accepted pathophysiology.

Classifications are designed to adapt and respond to changes in clinical practice and knowledge of the disease. Although the Panama classification describes the pathogenesis and the pathophysiology of pediatric PHVD more fully, it is not commonly accepted yet and will likely undergo further modification in future consensus meetings such

***Corresponding author:** Matthias Gorenflo, Department of Ped. Cardiol and Congenital Cardiology, University Med. Ctr., Heidelberg, Germany, E-mail: matthias.gorenflo@med.uni-heidelberg.de

Received March 22, 2012; **Accepted** June 04, 2012; **Published** June 15, 2012

Citation: Gorenflo M, Mebus S, Adatia I, del Cerro MJ, Bonnet D, et al. (2012) Neonatal and Childhood Pulmonary Hypertension - An Update (2012). J Clin Exp Cardiolog S8:011. doi:10.4172/2155-9880.S8-011

Copyright: © 2012 Gorenflo M, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

1.	**Pulmonary Arterial Hypertension (PAH)**
1.1	Idiopathic PAH
1.2.	Heritable
1.2.1.	BMPR2
1.2.2.	ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3.	Unknown
1.3.	Drug- and toxin-induced
1.4.	Associated with
1.4.1.	Connective tissue diseases
1.4.2.	HIV infection
1.4.3.	Portal hypertension
1.4.4.	Congenital heart diseases
1.4.5.	Schistosomiasis
1.4.6.	Chronic hemolytic anemia
1.5.	Persistent pulmonary hypertension of the newborn
1´.	Pulmonary Veno-occlusive Disease (PVOD) and/or Pulmonary Capillary Hemangiomatosis (PCH)
2.	**Pulmonary hypertension owing to left heart disease**
2.1.	Systolic dysfunction
2.2.	Diastolic dysfunction
2.3.	Valvular disease
3.	**Pulmonary hypertension owing to lung diseases and/or hypoxia**
3.1.	Chronic obstructive pulmonary disease
3.2.	Interstitial lung disease
3.3.	Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4.	Sleep-disordered breathing
3.5.	Alveolar hypoventilation disorders
3.6.	Chronic exposure to high altitude
3.7.	Developmental abnormalities
4.	**Chronic Thromboembolic Pulmonary Hypertension (CTEPH)**
5.	**Pulmonary hypertension with unclear multifactorial mechanisms**
5.1.	Hematologic disorders: myeloproliferative disorders, splenectomy
5.2.	Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3.	Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4.	Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Table 1: Updated clinical classification of pulmonary hypertension (DANA POINT, 2008; ref. (1)).

as the forthcoming World Symposium on Pulmonary Hypertension to be held in Nice in February 2013.

Epidemiology

Among the different issues relating to pediatric PH, the etiology and epidemiology of the disease are two of the most important. When dealing with an orphan or rare disease a comprehensive approach is to develop registries to obtain data in a large number of patients [7]. The adult community has paved the way with several registries recently published [8-15]. There are several national registries and some data are also available from large therapeutic studies and databases. These data are essential to better define the different etiologies and their importance in pediatrics. We report hereafter the current data available for pediatric PH.

Incidence and prevalence

Patients with pulmonary hypertension associated with congenital heart disease (PAH-CHD) prior to corrective surgery as well as patients presenting with (neonatal) lung disease and PAH are currently not the focus or excluded from most registries. The various and current pediatric registries have different inclusion criteria and, therefore, not only are comparisons difficult but also, may not provide a complete picture of PH in children. PAH associated with CHD represents the most preventable cause of pulmonary vascular disease worldwide [16].

If care is centralized, as in France, UK and the Netherlands, it may be possible to report incidence and prevalence of PH in pediatrics. In France, a childhood PAH prevalence of 2.2 per million has been reported [17]. In the United Kingdom, the incidence of idiopathic PAH is estimated at 0.48 per million children and the prevalence at 2.1 per million children [18]. In a large registry cohort of 3263 Dutch patients, the annual incidence and point prevalence for idiopathic PAH has been reported at 0.7 and 4.4 per million children and 2.2 and 15.6 for PAH-CHD, respectively [19]. However, and this is true for all registries, it remains impossible to be sure that a complete diagnostic workup has been performed in all patients. Notwithstanding this uncertainty, most data derive from expert centers that apply strict inclusion criteria. Therefore, it may be assumed that the data reflect the true frequency of idiopathic PAH in the pediatric population in these countries with the caveat that unless genetic testing is performed in all cases the incidence of heritable PAH will be underestimated.

Pediatric etiologies

Extensive reviews on pathogenesis of PAH including neonatal PAH are available [20]. Therefore, this review will, not focus on pathogenesis. Likewise the differences between adults and children with respect to etiology, pathogenesis and treatment of PAH have been reviewed recently [21].

The recent recognition that some kinds of pulmonary hypertensive

1.	**Prenatal Or Developmental Pulmonary Hypertensive Vascular Disease.**
1.1.	*Associated with Maternal or Placental Abnormalities: chorioamnionitis, preeclampsia,…*
1.2.	*Associated with Fetal Pulmonary Vascular Maldevelopment: congenital alveolar dysplasia,..*
1.3.	*Associated with Cardiac Fetal Maldevelopment: premature closure of PDA/F.ovale, obstructed TAPVR*
2.	**Perinatal Pulmonary Vascular Maladaptation (PPHN)**
2.1.	*Idiopathic PPHN.*
2.2.	*Associated with or triggered by: sepsis, meconium, CHD, diaphragmatic hernia trisomies,diazoxide,..*
3.	**Pediatric Cardiovascular Disease**
3.1.	*Systemic to Pulmonary shunts.*
3.2.	*Postoperative PAH After Shunts Closure, Repair of D-TGA, Fallot, Left Heart Obstruction,…*
3.3.	*Pulmonary Vascular Disease following Staged Palliation For Single Ventricle Physiology.*
3.4.	*PVD Associated with Congenital Abnormalities of Pulmonary Arteries or Veins.*
3.5.	*Pulmonary Venous Hypertension*
4.	**Bronchopulmonary Dysplasia**
4.1.	*Associated with Pulmonary Vascular Hypoplasia.*
4.2.	*Associated with Pulmonary Vein Stenosis.*
4.3.	*Associated with Left Ventricular Diastolic Dysfunction.*
4.4.	*Associated with Systemic to Pulmonary shunts (PDA, ASD, VSD, aorto pulmonary collaterals).*
4.5.	*Associated with Significant Hypercabia and/or Hipoxia.*
5.	**Isolated Pediatric Pulmonary Hypertensive Vascular Disease.**
5.1.	*Idiopathic.*
5.2.	*Heritable.*
5.3.	*Drugs and toxins*
5.4.	*Pulmonary Veno-occlusive Disease and Pulmonary Capillary Hemangiomatosis*
6.	**Multifactorial PVD in Congenital Malformation Syndromes.**
6.1.	*With Associated Congenital Heart Disease.*
6.2.	*Without Associated Congenital Heart Disease.*
7.	**Pediatric Lung Disease:** *Cystic fibrosis, interstitial lung disease, sleep disordered breathing…*
8.	**Pediatric Thromboembolic Disease.**
9.	**Pediatric Hypobaric Hypoxic Exposure.**
10.	**Pediatric Pulmonary Vascular Disease Associated With Other System Disorders: portal hypertension, hematological, oncological, metabolic, autoimmune disorders…**

Table 2: Classification of pediatric Pulmonary Hypertensive Vascular Disease (PHVD) - Panamá Classification 2011. Abbreviated schema according to (3).

vascular disease may have similarities with malignant disorders, the monoclonal and polyclonal proliferation of abnormal endothelial cells in idiopathic PAH versus Eisenmengers complex suggest that there may be differences in diseases with apparently similar histology and raise the possibility that not all treatments are equally efficacious in all clinical phenotypes [22,23].

The Swiss registry included patients aged from 28 days to 18 years seen between 1999 and 2005. Out of 23 patients, idiopathic/familial was the etiology in 8 (34.8%), CHD in 12 (52.2%) and associated with pulmonary disease in 3 (13%) [24]. The treatment and survival of children with PAH referred to the UK PH service has ben investigated [25]: among the 216 patients treated between 2001 and 2006, 60 had idiopathic PAH (mean age 7.4 years, 47 (62%) were female) whereas 156 had associated forms of PAH (mean age 7.9, 80 (51%) female). 8% had a family history of PAH. Among the associated forms, 49 had Eisenmenger, 47 post cardiac repair, 29 lung disease, 9 connective tissue disease, 14 miscellaneous and 8 had complex CHD.

The French registry [17] describes that 60% had idiopathic PAH, 10% familial PAH, 24% PAH associated with CHD (excluding those directly related to CHD), 4% PAH associated with connective tissue disease and 2% portal hypertension.

Data obtained from the national referral centre for pediatric PH in the Netherlands showed that between 1993 and 2007, 63 patients (mean age 5.8 years,62% female) presented with PH of which 18 were idiopathic [26]. In 45 patients, more than one cause was found: 40 had CHD, 2 connective tissue diseases, 17 lung diseases and 1 chronic thromboembolic disease. Of interest is that in this group of 45, 11 patients with associated conditions had a level of PH not sufficiently explained by these conditions and were ultimately classified as having idiopathic PAH. This resulted in a final count of 29 (46%) idiopathic, 23 (37%) CHD, 2 (3%) connective tissue disease, 8 (12%) lung disease and 1 (2%) thromboembolic disease. The authors' raised an important point, which also had been suggested by others [3], that children often have multiple contributors to PAH and, therefore, are not easily categorised within the Dana point system.

Data from the pediatric REVEAL registry, including 216 patients (mean age at diagnosis: 8.0 years) demonstrated that idiopathic PAH and associated PAH patient represented 92% (122 idiopathic, 77 CHD). Ten patients had connective tissue disease, 3 portopulmonary , 3 persistent pulmonary hypertension of the newborn and 1 another associated form [27].

The TOPP, short for Tracking Outcome and Practice in Pediatric Pulmonary Hypertension, is an international, multicenter, prospective, observational, non-interventional program set up to study the natural history of PH, focusing on diagnosis and disease management in children and adolescents in real-world clinical settings. A registry analysis from the Netherlands showed that 317 (88%) patients had (PAH), which was idiopathic or familial PAH in 182 (57%), and associated with other disorders in 135 (43%), of which 115 (85%) cases were associated with CHD [28]. 42 patients (12%) had pulmonary hypertension associated with respiratory disease or hypoxaemia,

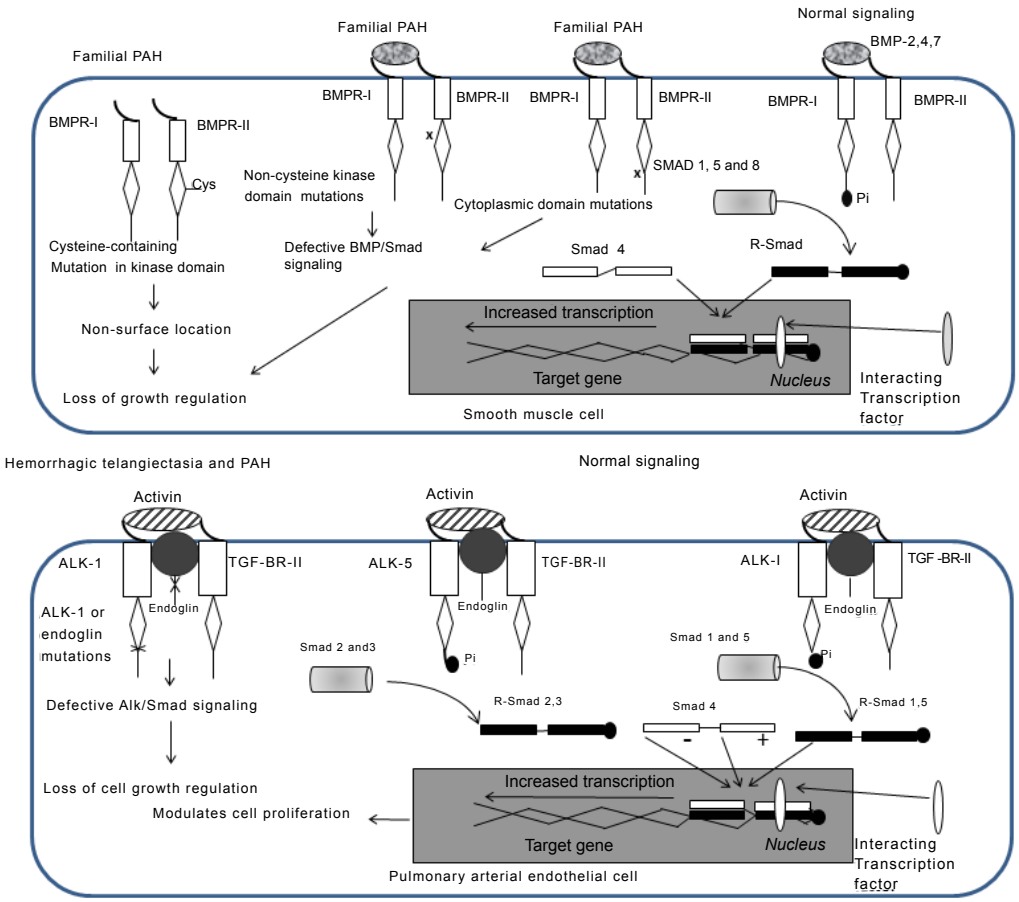
Citation: Gorenflo M, Mebus S, Adatia I, del Cerro MJ, Bonnet D, et al. (2012) Neonatal and Childhood Pulmonary Hypertension - An Update (2012). J Clin Exp Cardiolog S8:011. doi:10.4172/2155-9880.S8-011

with bronchopulmonary dysplasia being the most frequent, and three patients had chronic thromboembolic pulmonary hypertension, or miscellaneous causes of pulmonary hypertension.

In summary PAH is a more heterogeneous condition in children than adults and more frequently associated with genetic syndromes. In addition PAH is more likely to be complicated by degrees of CHD and pulmonary disease, which on their own, would be unlikely to cause severe PAH.

Genetics of pulmonary hypertension

Pulmonary hypertensive vascular disease is associated with endothelial damage proliferation of smooth muscle cells, as well as dysfunction and resistance to apoptosis of vascular and perivascular cells. Research focusing on genetic determinants that influence proliferation has led to the discovery of heterozygous germline mutations in the gene encoding for bone morphogenetic protein type II receptor (BMPR-II) more than ten years ago [29,30]. BMPR-II is a type II receptor member of the transforming growth factor – beta (TGF-β) superfamily. The gene encoding for BMPR-II is located on chromosome 2q33. Three different BMP receptors type I and three BMP receptors type II are known. They function as serine/threonine kinases. BMPs play an important role during embryonic development especially in connective tissue (chondrogenesis) [31]. In a smaller proportion of PAH patients mutations in other genes that participate in the BMPR-II signaling pathway such as Activin A receptor type II-like kinase-1 (ACVRL1 or ALK-1), Endoglin [32] and SMAD [33] have been described (Figure 1)[34]. In patients with heritable pulmonary arterial hypertension (HPAH) mutations in the BMPR-II gene have been found in 58% - 74% of patients with familial PAH [35-38]. Patients presenting with apparently sporadic PAH show BMPR-II mutations in about 10 – 40% [39]. More than 300 mutations in the BMPR-II gene have been described thus far [35,40]. The mutations have been identified in various exons of the BMPR-II gene. 30 % of mutations are missense mutations [39] leading to substitutions of highly conserved amino acids with functional impact on the ligand-binding or kinase domains. The remaining 70% of other known mutations are frameshift or nonsense mutations, gene rearrangements or splice-site defects, all of them resulting in premature termination of the transcript. In female patients with HPAH, missense mutations in the BMPR-II gene are associated with earlier disease onset compared to patients with truncating mutations [41]. Mutation carriers show a variable disease penetrance, only 20% of mutation carriers develop clinical disease [42,43]. Carriers of the BMPR-II mutation often transmit the risk



Reproduced with permission from [34].

Figure 1: Mutations in BMPR2 and ALK-1 in the development of idiopathic pulmonary arterial hypertension. Top Diagram: In the normal vascular smooth muscle cell binding of the BMP ligand to the complex of BMPR-I and BMPR-II and subsequent phosphorylation of Smad 1, 2 and 8 modulates transcription resulting in growth arrest. Mutations BMPR-II lead to defective Smad signaling resulting in increased cell proliferation.

Bottom Diagram: In pulmonary endothelial cells mutations in both ALK-1 and endoglin finally promote loss of cell growth regulation. A mechanism which is also involved in hemorrhagic telangiectasia.

to their progeny but the majority of carriers will not develop PAH [44]. Genetic counseling of patients and/or parents must take this into account. Patients with PAH and BMPR-II mutations differ from those with IPAH without mutations and are younger at diagnosis with more severe disease as reflected by hemodynamics [40]. This may be explained by additional genetic, epigenetic or environmental factors that contribute to disease manifestation. Differential expression of the estrogen metabolizing gene CYP1B1 has been found to modify the risk for manifest FPAH [45] underlining the role of additional genetic factors in pathogenesis of PAH. Despite these advances the specific critical pathway for the development of the disease is unknown. Mouse models of BMPR-II mutation offer the possibility to, not only, to elucidate disease mechanisms further, but also, to facilitate preclinical testing of new pharmacological products [46]. The role of BMPR-II in patients with APAH is unsettled: An increased frequency of BMPR2 mutations in patients with PAH-CHD has been reported [47] whereas others were unable to demonstrate such a correlation in Eisenmenger patients with atrial septal defect [48]. Associated genetic abnormalities such as somatic chromosome abnormalities have been described and indicate that a second genetic hit may contribute to the disease progression in patients with PAH and BMPR-II mutations [49].

Biomarkers of pulmonary hypertension

Proliferation and tissue remodeling are hallmarks of pulmonary vascular disease [20]. Current research focuses on biomarkers that reflect the ongoing disease process.

Atrial natriuretic peptide (ANP) and b-type natriuretic peptide (BNP) which is produced in atrial and ventricular myocardium are elevated in association with pressure overload and therefore have been found to be elevated in pulmonary artery hypertension. NT-proBNP could be superior to BNP as a survival parameter in patients with PH (different etiologies) because it may reflect both hemodynamic impairment and renal insufficiency and indicate increased likelihood of mortality [50]. Several studies in children with IPAH and APAH have shown that BNP [51] and NT-proBNP [52] correlate with functional status in children with PAH and that norepinephrine and NT-proBNP were highly predictive for mortality [52]. In children with IPAH and APAH serial measurements of BNP were found to correlate with changes in hemodynamic and echocardiographic changes in a given patient [53].

Endogenous tissue inhibitors of matrix metalloproteinases (TIMPs) control the activity of extracellular matrix (ECM)-degrading metalloproteinases (MMPs). A recent study showed that increased TMP-4 correlated with higher class of functional impairment in adult patients with IPAH, APAH and PAH associated with thrombotic or embolic diseases (CTEPH) [54].

Circulating endothelial progenitor cells (EPCs; CD34+/KDR+ and CD34+/KDR+/CD31+/CD45-) have been found to be reduced by about 50% in patients with three forms of PAH (idiopathic/heritable, drug-induced, and connective tissue disease) [55]. Similar results were found in IPAH and Eisenmenger patients [56], while other groups have found differently characterized (CD133+) cells to be increased in the lung and circulation of PAH patients [57]. In a pilot study, an EPC capture chip has been used as a rapid bedside test for the screening and monitoring of patients with PAH [55].

Soluble biomarkers such as Endothelin-1, von Willebrand factor, metabolites of the eicosanoid pathway or measurement of circulating endothelial progenitor cells and circulating endothelial cells are of special interest [54]. Larger series analyzing the role of biomarkers in diagnosis and monitoring of patients with PAH are clearly necessary [58].

Diagnosis

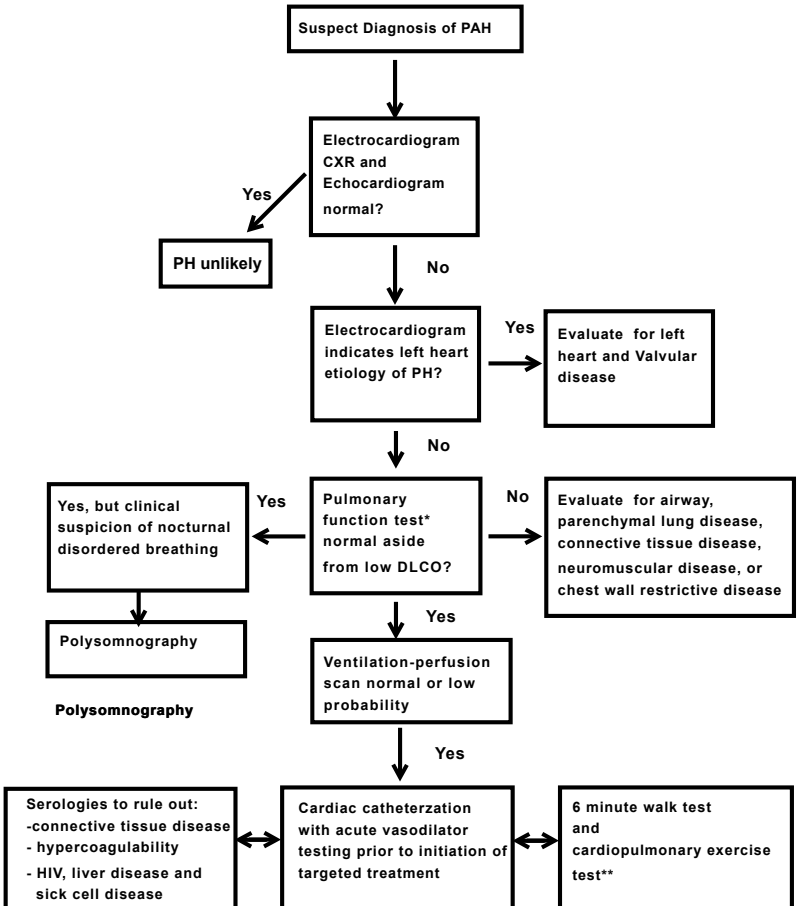
The purpose of a diagnostic work-up in Pulmonary Arterial Hypertension (PAH) is to confirm the diagnosis and assess the severity of PAH by identifying the underlying conditions, evaluate pulmonary vasoreactivity and right ventricular function. Thus, consensus guidelines for screening, detecting and diagnosing PAH include a complex sequence of diagnostic tools [2,59,60]. The evidence for these guidelines was derived from studies in adults and frequently in subgroups other than PAH associated with CHD (PAH-CHD). However, in the absence of clinical guidelines focusing on pediatric PAH-CHD, these patients are currently managed with the same diagnostic paradigm as the adults, on which recently published recommendations for children are based upon [61].

PAH in children is a rare disease and in the initial stages symptoms are mild and nonspecific and diagnosis is challenging. Misinterpretation of symptoms and diagnostic findings typically delays diagnosis. Diagnosis may be delayed even when congenital heart disease is the cause of PAH. Early diagnosis is crucial as selected children with PAH-CHD may show a favorable response to targeted pulmonary hypertension drugs and may become eligible for surgical repair [62-64]. However, the "treat and repair" strategy remains to be validated, especially the long term results [65]. Early treatment of PAH may be beneficial for adolescents and adult patients [66]. Pediatric PH can present with multiple problems and may be associated with more than one underlying condition [26]. Therefore, a complete and immediate diagnostic evaluation of children with suspected PAH in a tertiary centre with expert knowledge in both -CHD and PAH- is recommended [21,61,67].

Within the last decade there has been substantial progress in diagnostic technology particularly thoracic and cardiac imaging modalities [68]. Diagnostic algorithms start with general non-invasive screening tests and lead sequentially to invasive diagnostics, specific functional tests, finally culminating in cardiac catheterization [2, 61]. The indication for cardiac catheterization must be balanced in each individual patient against potential complications such as hemodynamic compromise and, therefore, should be performed only in tertiary centers familiar with the procedure with a specific team (especially anesthesiologists) with expertise.

A detailed medical history followed by a thorough physical examination are the keystones in the evaluation of a child with suspected PAH (Figure 2). Patient or parental history often reveals nonspecific symptoms such as dyspnea, syncope, recurrent upper respiratory tract infections, poor appetite and feeding difficulties with failure to thrive and in advanced stages, signs of heart failure [69]. In patients with pediatric PAH-CHD symptoms vary with the specific cardiac lesion, patients´ age, prior corrective surgery, magnitude and direction of the shunt as well as the severity of PAH [19,70].

Initial diagnostic routine screening tests include electrocardiogram (ECG) and chest x-ray (CXR). While ECG in idiopathic PAH (IPAH) patients shows right ventricular hypertrophy and right axis deviation, its sensitivity and specificity are inadequate for detecting PAH particularly in pediatric CHD patients [71]. In addition, the role of Holter monitoring in the diagnostic algorithm has not been established,



*If unable to obtain a reliable test in a young child and there is a high index of suspicion for underlying lung disease, the patient may require further lung imaging.
**Children older than 7 years of age can usually perform reliably to assess exercise tolerance with cardiopulmonary exercise testing in conjunction with diagnostic work-up. The 6-minute walk test may be less useful in many children.
Reproduced with permission from (**69**).

Figure 2: Diagnostic algorithm in children with suspected PH.

although in adult CHD patients with severe PAH, rhythm disturbances are associated with a poor prognosis [56]. Although 90% of PAH patients have abnormal findings on CXR, there is little correlation with severity of PAH. A normal CXR does not allow the exclusion of PAH with certainty [72].

In PAH-CHD, imaging is pivotal to confirming the diagnosis. Echocardiography is non-invasive, provides information about structural CHD, myocardial function, and may allow estimation of intracardiac and pulmonary pressure. However it depends on adequate windows, patient cooperation and expert interpretation of findings [68]. Besides indirect cardiac signs of PAH (e.g. increased tricuspid regurgitation, right atrial and ventricular enlargement), there have been new echocardiographic measuring parameters explored within the last years such as analysis of contraction timing, myocardial tissue Doppler, Tei-Index, tricuspid annular plane systolic excursion (TAPSE), strain and strain rate. These help to recognize early right ventricular dysfunction [73,74]. Echo analysis of right ventricular morphology and function remains difficult because of the morphology and position of the right ventricle. Although data in pediatric patients are limited, cardiac magnetic resonance imaging (MRI) can provide additional information on morphology, function, and metabolism of the heart including the right ventricle [61]. Referring to this, age- and gender-matched reference values for right atrial and right ventricular hemodynamics in healthy probands have been published [75,76]. In addition, new MRI technologies offer assessment of hemodynamic parameters in the pulmonary circulation such as lung perfusion and may even replace invasive procedures in the future [59,77]. However it has to be kept in mind that MRI requires general anesthesia in many children - especially if the MR protocol requires a breath hold - which requires careful and expert anesthetic management.

The diagnosis PAH should be confirmed by cardiac catheterization to measure PA pressure, wedge or left atrial pressure and pulmonary blood flow and calculate pulmonary vascular resistance. It is recommended that cardiac catheterization and vasoreactivity testing should be performed at institutions with considerable experience in this field to minimize adverse events [74].There are different criteria for acute vasodilator response (AVR) [78,79]. At present there is no consensus but many authorities would define a positive acute pulmonary vascular reactivity test as follows:

A) Patients without an unrestricted shunt at the ventricular or ductal level: PAPm decrease ≥ 20% and no cardiac index

decrease (within 5% from baseline).

B) Patients with an unrestricted shunt at the ventricular or ductal level: PAPm decrease ≥ 20% and no cardiac index decrease (within 5%) or PVRI decrease ≥ 25% and no cardiac index decrease (within 5%) [78].

Results of vasoreactivity testing in patients with PAH-CHD prior to intracardiac repair are useful to decide on operability [64]. Pulmonary to systemic resistance ratios > 0.2-0.3 or PVRI > 6 – 8 Wood units *m^2 during acute vasodilator testing suggest an increased risk of early right ventricular failure and/or late postoperative PHVD [64,80,81].

In childhood PAH-CHD pulmonary function tests and exercise tests provide useful information during follow-up. The 6-min walk test (6MWT) is used to assess maximum exercise tolerance whereas cardiopulmonary exercise testing (CPET) should be used as a complementary test in children when the 6MWT distance is >300 m [82]. Limitations of such functional tests are patient age and validation for children with PAH. Laboratory analysis is useful to identify anaemia, hemolysis, liver, or thyroid dysfunction, coagulation abnormalities, connective tissue disease and, if indicated, HIV infection.

Medical Treatment

Treatment guidelines for adult PAH have been published [60,72,83]. However, their evidence is based on studies in adults or children >12 years old predominantly with idiopathic/ familial PAH. There are limited data for children <12 years of age. Recommendations for children with PAH-CHD are derived from therapeutic algorithms of PAH-CHD in adults.

Currently, treatment options are targeted drugs with an impact on one of three pulmonary vascular endothelial-based pathways: endothelin-1, nitric oxide, and prostacyclin pathways [84]. The primary aim of these drugs is reduction of clinical symptoms, improved quality of life and prolonged survival [85]. It remains unknown whether they modify the fundamental disease process. As there are few randomized controlled studies for drug therapy in pediatric patients with PAH-CHD, the following data are based predominantly on anecdotal reports, case series and observational reports. Notably, although there is an increasing amount of data for PAH-CHD in children showing a short-term benefit of targeted therapies, there are no long-term trials of treatment efficacy and outcome in this specific pediatric population. Moreover, except for bosentan and sildenafil, there are no targeted drugs which have been approved for the treatment of PAH in children in Europe. Before starting therapy with these drugs, careful consideration of potential benefits and risks as well as specific clinical expert knowledge with pediatric PAH should be warranted.

Endothelin-1 (ET-1) Receptor Antagonists

Endothelin-1 is a potent vasoconstrictor with elevated concentrations in the plasma and lung tissue of patients with PAH. There are two ET-1 receptor subtypes, ET_A and ET_B, mediating the activity of ET-1. Increased endothelin levels have been found inconsistently in patients with PAH-CHD [86-88]. Increased endothelin levels have been correlated to a decreased pulmonary clearance after congenital heart surgery in patients with PAH-CHD [89-91]. In addition, to date there is still no meaningful evidence demonstrating receptor selectivity as clinically relevant [92].

Bosentan is an oral non-selective endothelin receptor antagonist which is explicitly approved for the treatment of severe PAH related to congenital systemic-to-pulmonary shunts and Eisenmenger's physiology [93]. There is a correlation between a decrease in indexed PVR and arterial ET-1 levels in response to the ETA - receptor antagonist BQ123 but at present there is no evidence for and advantage of using selective ETA - receptor antagonist compared to bosentan. In July 2009, a pediatric formulation of bosentan has become available in Europe for children with an age of at least 2 years [94].

The use of bosentan has been reported more frequently in childhood PAH than other oral PAH therapies [95]. Most of the clinical studies and observations have not differentiated between the underlying etiology of PAH within the analysis [93,96] and, therefore, no clear conclusions could be drawn for each PAH subpopulation. Moreover, the observation periods were mostly brief (weeks to months) with small case-numbers.

Available data for bosentan in infantile PAH-CHD demonstrated symptomatic improvements [97], beneficial effects in clinical status, functional class [97] and pulmonary hemodynamics after a follow-up of approximately 1 year.

However, some studies suggest that after 2 years the beneficial effects of bosentan decline more often in children than adults [99,100].

Bosentan appears to be safe and well tolerated in children and elevation transaminases is less often observed than in adults [93,97].

Among selective oral ET_A receptor antagonists [101,102], ambrisentan has demonstrated efficacy and safety in the adult PAH population [102]. Specific data for PAH-CHD are limited in adults and children. Ambrisentan improves exercise capacity and functional class in adult PAH-CHD patients [103] but pediatric data for PAH-CHD are currently unavailable.

Phosphodiesterase type 5 (PDE-5) inhibitors

PDE-5 inhibitors are vasodilators with predominantly pulmonary, but also systemic effects. They are antiproliferative and inhibit platelet aggregation [104]. PDE-5 is highly expressed in the hypertrophied human right ventricle, and PDE-5 inhibition may improve myocardial contractility [105].

Currently, there are three different PDE-5 inhibitors (Sildenafil, Vardenafil and Tadalafil) which have been studied in patients with PAH. Sildenafil and Tadalafil have shown pulmonary selectivity, whereas only sildenafil improved arterial oxygenation [106]. Of note, the clinically used PDE-5 inhibitors are not exclusively selective for PDE-5 but may also inhibit PDE-1 or PDE-3, and other isoforms of the enzyme.

Current studies in pediatric PAH are limited by a short follow-up-time and overall a lack of randomized controlled studies. Pilot studies suggest efficacy and safety of sildenafil in children with PAH-CHD showing improvement in functional class, exercise capacity, and hemodynamics up to 1 year [107-108]. These benefits seem to persist for at least two years [109]. Sildenafil dosing in children is controversial. A recent study suggested that low dose sildenafil was ineffective [27]. However, another study suggested that low-dose oral sildenafil (0.5 milligrams per kilogram per day) was associated with early clinical and hemodynamic improvement up to 3 months as sufficient [110].

A recent study (STARTS-1) in 235 children (≥8 kg) showed efficacy, safety, and tolerability of oral sildenafil in children with IPAH and PAH-CHD [27]. STARTS-1 completers could enter the STARTS-2 extension [111]. In this study dose adjusted for bodyweight were used as follows:

- 8 kg to 20 kg: 10 mg/dose TID PO
- 20.1 to 45 kg: 20 mg/dose TID PO
- > 45 kg: 40 mg/dose TID PO.

Based on these data (http://clinicaltrials.gov: A1481131), sildenafil has been approved in Europe since May 2011 for children with an age of at least 1 year. The current European dosing recommendations for patients aged ≥ 1 year to 17 years are as follows:

- Patient body weight ≤ 20 kg: 10 mg/dose TID PO.
- Patient body weight > 20 kg: 20 mg/dose TID PIO.

Higher than recommended doses should not be used, until more data are available in pediatric patients with PAH because there was an increased mortality in the high dose group. Further investigation is warranted to determine optimal dosing based on age and weight. Sildenafil is finding a place in critical care settings. Oral sildenafil attenuates rebound pulmonary hypertension in children under 5 years of age with severe PH [112] and facilitated successful postoperative withdrawal from inhaled nitric oxide in children with PH following cardiac surgery [113,114].

Intravenous sildenafil has been approved for use in adults by the FDA and EMA. Intravenous sildenafil decreased PA pressures and shortened the ICU stay in pediatric patients undergoing congenital heart surgery [115]. Higher doses of sildenafil cause systemic hypotension and if administered to patients with near normal PA pressures the intrapulmonary shunt increases and oxygenation decreases [116,117]. Limited data in 33 children demonstrated that Tadalafil can be safely used for pediatric patients with PAH [118].

Prostacyclin and Prostacyclin Analogues

Prostacyclin is a potent pulmonary and systemic vasodilator with antiplatelet activity, and appears to have inotropic effects, endothelial cell stabilization and antiproliferative effects when used long-term [119]. Prostacyclin and longer acting analogues are administered by continuous infusion intravenously or subcutaneously [120] or by intermittent inhalation. Intravenous epoprostenol has been demonstrated to improve outcomes in children with IPAH and PAH-CHD [121]. Inhaled iloprost has the advantage of a longer half-life and may require fewer inhalations. However, it is often not possible to achieve high enough doses with intermittent inhalations in severely ill children [122,123]. Subcutaneous Treprostinil has been used as rescue therapy for in children with refractory pulmonary arterial hypertension in a small series [120].

Combination Therapy

For symptomatic patients who failed to improve with mono-drug treatment, combination therapy may exert synergistic effects through targeting different molecular pathways [124]. Unfortunately, randomized-controlled trials in children with PAH-CHD are lacking, although in clinical settings more and more children receive combination therapies [84], perhaps supporting general effectiveness, safety and tolerability [125].

In adults, recently one randomized, placebo-controlled, double-blinded trial with combination therapy of bosentan and sildenafil in Eisenmenger patients (n = 21) has been published. After a relative short period of 3 months, treatment with bosentan significantly improved walking distance and pulmonary hemodynamics, while adding sildenafil to bosentan did not cause significant effects [126]. Sildenafil and bosentan may affect blood levels of each drug and dose adjustments may be required during combination therapy [127].

The optimal timing of combination therapy remains unclear. The financial implications of expensive combination therapy need careful consideration.

Investigational Therapies

Even though available pulmonary vasodilatory drugs showed beneficial effects in pediatric PAH by improving symptoms, PAH remains a fatal disorder [128]. Alternative approaches undergoing evaluation at present include:

New substances that address specific receptors mediating pulmonary vasodilation such as the selective prostacyclin receptor (IP receptor): Selexipag an oral, selective IP receptor agonist has been studied in a Phase II proof-of-concept study [129].

Direct stimulators of soluble guanylate cyclase (sGC) such as Riociguat (BAY 63-2521) are under investigation [130]. Direct stimulation of soluble guanylate cyclase (sGC) has the potential (yet theoretical) advantage of being independent of endogenous nitric oxide synthesis.

Newer agents with novel targets such as cell proliferation, inflammatory and immune pathways [20,85,131] may have the potential to reverse pulmonary vascular remodelling, restore the endothelial function and to reverse PAH [85].

These approaches have shown encouraging results in preclinical animal models and application to human disease is being considered [20,125,131-133].

Follow-up of children with PAH

Follow-up of children with PAH remains challenging as the available tools used in the adult population are either not suitable for small children or have not been evaluated for children in this condition. The aim of the follow-up is to organize a regular evaluation of children with PAH with focus on variables with prognostic importance, i.e. variables that assess disease severity, stability and indicate prognosis. Indeed, follow-up and patient status assessment will rely on information derived from a panel of tests including clinical evaluation, exercise tests, biochemical markers, and echocardiographic and hemodynamic assessments [60,134]. Limited data are available on this panel of markers in pediatric PAH. Heart rate recovery at one minute of rest (HRR1) after 6-minute walk test is a strong predictor of clinical worsening in adult patients with IPAH [135].

As indicated in the currently available guidelines, the clinical condition of a child can be defined as stable and satisfactory, stable but not satisfactory, unstable and deteriorating. In clinical practice, clinical deterioration is easy to identify when right ventricular failure or syncope are apparent. Conversely, assessing exercise performance by the 6MWT or by cardiopulmonary exercise testing has many limitations related to age and availability [136]. Echocardiographic parameters that reflect right ventricular function such as TAPSE and the presence of pericardial effusion may be useful but the prognostic significance has not evaluated in children Normal values for TAPSE in children, with age specific percentiles, are available [137]. Exploratory studies are ongoing to determine which combination of functional and morphological RV parameters might be useful to collect. Finally, repeat cardiac catheterization to obtain hemodynamic measurements in cases with an uncertain response to therapy is important if additional

therapy is available. Routine right heart catheterization to confirm improvement with treatment is more debatable. As in adults, it is of utmost importance that children with PAH are regularly followed in a pediatric PAH referral center that have facilities, skills and a sufficient volume of patients to obtain the best outcomes.

Despite the use of a panel of relevant biomarkers, it is difficult to predict the time to clinical worsening in pediatric PAH. Indeed, treating children according to the concept of "goal-oriented" treatment or "treat to target" is limited by the availability and validation of the currently used biomarkers. Whether or not this strategy is applicable to infants and children with PAH remains unclear. Defining age-adapted composite endpoints of therapy that may predict clinical worsening would be of great help. Recently published data on survival in pediatric PAH in the current era of targeted PAH treatments demonstrated improvement of survival with PAH therapies compared to predicted survival based on historical cohorts [25]. Data from the Dutch registry reveals that, since the introduction of second-generation drugs, only selected children demonstrated improved survival [138]. These findings suggest that current therapy remains suboptimal and that earlier more aggressive use of combination therapy, based on a composite of clinical endpoints and biomarkers to assess response to therapy are needed to recognize insufficient improvement and to predict future deterioration.

Summary

Neonatal and childhood pulmonary hypertensive vascular disease presents unique challenges in diagnosis, classification, functional assessment and drug trials. Recent epidemiological studies are beginning to highlight the differences between childhood and adult disease. There are unique symptom complexes and disease phenotypes which require a comprehensive classification system to improve diagnosis and to understand the effect of therapies in different age and diagnostic groups. Age and developmentally appropriate outcome measures and biomarkers require further investigation so that we avoid missing important therapeutic effects not apparent in children too young to undertake for instance a 6 minute walk or too sick to undergo cardiac catheterization. The prenatal origins of pulmonary vascular disease and importance of vascular hypoplasia and maldevelopment form an important but under investigated aspect of the phenotype and disease progression in childhood. Nevertheless the availability of 5 different classes of drugs with which to treat children with PH is a remarkable advance over the last 30 years. Given that most referral centers will see relatively few patients with PHVD, imaginative and collaborative approaches to drug evaluation in children will be required in the future. Currently combination therapy and the impact on pathological signaling pathways may offer the best hope of improving quality of life and survival. Reversal of the abnormal endothelial cell and smooth muscle interface remains elusive.

Although substantial advances have been made in our understanding of pulmonary hypertensive vascular disease there remain important challenges to overcome in designing pediatric drug trials and to improve long term survival.

Funding

This work was not funded by any grant. There were no fees or support of industry to any of the authors for writing this manuscript.

References

1. Simonneau G, Robbins I, Beghetti M, Channick RN, Delcroix M, et al. (2009) Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 54: S43-S54.
2. Badesch DB, Champion HC, Sanchez MA, Hoeper MM, Loyd JE, et al. (2009) Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 54: S55-S66.
3. Cerro MJ, Abman S, Diaz G, Heath Freudenthal A, Freudenthal F, et al. (2011) A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: report from the PVRI Pediatric Taskforce, Panama 2011. Pulm Circ 1: 286-298.
4. Goldberg DJ, French B, McBride MG, Marino BS, Mirarchi N, et al. (2011) Impact of oral sildenafil on exercise performance in children and young adults after the Fontan operation: a randomized, double-blind, placebo-controlled, crossover trial. Circulation 123: 1185-1193.
5. Giardini A, Balducci A, Specchia S, Gargiulo G, Bonvicini M, et al. (2008) Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients. Eur Heart J 29: 1681-1687.
6. Hirono K, Yoshimura N, Taguchi M, Watanabe K, Nakamura T, et al. (2010) Bosentan induces clinical and hemodynamic improvement in candidates for right-sided heart bypass surgery. J Thorac Cardiovasc Surg 140: 346-351.
7. McLaughlin VV, Suissa S (2010) Prognosis of pulmonary arterial hypertension: the power of clinical registries of rare diseases. Circulation 122: 106-108.
8. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, et al. (2006) Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 173: 1023-1030.
9. Peacock AJ, Murphy NF, McMurray JJ, Caballero L, Stewart S (2007) An epidemiological study of pulmonary arterial hypertension. Eur Respir J 30: 104-109.
10. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, et al. (2010) Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest 137: 376-387.
11. McGoon MD, Krichman A, Farber HW, Barst RJ, Raskob GE, et al. (2008) Design of the REVEAL registry for US patients with pulmonary arterial hypertension. Mayo Clin Proc 83: 923-931.
12. Jing ZC, Xu XQ, Han ZY, Wu Y, Deng KW, et al. (2007) Registry and survival study in chinese patients with idiopathic and familial pulmonary arterial hypertension. Chest 132: 373-379.
13. Tueller C, Stricker H, Soccal P, Tamm M, Aubert JD, et al. (2008) Epidemiology of pulmonary hypertension: new data from the Swiss registry. Swiss Med Wkly 138: 379-384.
14. Fischler M, Speich R, Dorschner L, Nicod L, Domenighetti G, et al. (2008) Pulmonary hypertension in Switzerland: treatment and clinical course. Swiss Med Wkly 138: 371-378.
15. Frost AE, Badesch DB, Barst RJ, Benza RL, Elliott CG, et al. (2011) The Changing Picture of Pulmonary Arterial Hypertension (PAH) Patients in the United States: How the REVEAL Registry Differs From Historic and Non-US Contemporary Registries. Chest 139: 128-137.
16. Adatia I, Kothari SS, Feinstein JA (2010) Pulmonary hypertension associated with congenital heart disease: pulmonary vascular disease: the global perspective. Chest 137: 52S-61S.
17. Fraisse A, Jais X, Schleich JM, Di Filippo S, Maragnès P, et al. (2010) Characteristics and prospective 2-year follow-up of children with pulmonary arterial hypertension in France. Arch Cardiovasc Dis 103: 66-74.
18. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG (2010) Childhood idiopathic pulmonary arterial hypertension: a national cohort study. Heart 96: 1401-1406.
19. van Loon RL, Roofthooft MT, Hillege HL, Ten Harkel AD, van Osch-Gevers M, et al. (2011) Pulmonary hypertension in the Netherlands: Epidemiology and characterization during the period 1991 to 2005. Circulation 124: 1755-1764.
20. Archer SL, Weir EK, Wilkins MR (2010) Basic science of pulmonary arterial hypertension for clinicians: new concepts and experimental therapies. Circulation 121: 2045-2066.
21. Barst RJ, Ertel SI, Beghetti M, Ivy DD (2011) Pulmonary arterial hypertension: a comparison between children and adults. Eur Respir J 37: 665-677.
22. Lee SD, Shroyer KR, Markham NE, Cool CD, Voelkel NF, et al. (1998) Monoclonal endothelial cell proliferation is present in primary but not secondary pulmonary hypertension J Clin Invest 101: 927-934.

23. Rai PR, Cool CD, King JA, Stevens T, Burns N, et al. (2008) The cancer paradigm of severe pulmonary arterial hypertension. Am J Respir Crit Care Med 178: 558-564.

24. Fasnacht MS, Tolsa JF, Beghetti M (2011) The Swiss registry for pulmonary arterial hypertension: the paediatric experience. Swiss Med Wkly 137: 510-513.

25. Haworth SG, Hislop AA (2009) Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001-2006. Heart 95: 312-317.

26. van Loon RL, Roofthooft MT, van Osch-Gevers M, Delhaas T, Strengers JL, et al. (2009) Clinical characterization of pediatric pulmonary hypertension: complex presentation and diagnosis. J Pediatr 155: 176-82.

27. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, et al. (2012) Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation. 125: 113-122.

28. Berger RM, Beghetti M, Humpl T, Raskob GE, Ivy DD, et al. (2012) Clinical features of paediatric pulmonary hypertension: a registry study. Lancet 379: 537-546.

29. Deng Z, Morse JH, Slager SL, Cuervo N, Moore KJ, et al. (2000) Familial primary pulmonary hypertension (Gene PPH1) is caused by mutations in the bone morphogenetic protein receptor-II gene. Am J Hum Genet 67: 737-744.

30. International PPH Consortium, Lane KB, Machado RD, Pauciulo MW, Thomson JR, Phillips JA 3rd, et al. (2000) Heterozygous germline mutations in BMPR2, encoding a TGF-beta receptor, cause familial primary pulmonary hypertension. Nat Genetics 26: 81-84.

31. Bhatia M, Bonnet D, Wu D, Murdoch B, Wrana J, et al. (1999) Bone morphogenetic proteins regulate the developmental program of human hematopoietic stem cells. J Exp Med 189: 1139–1148.

32. Trembath RC, Thomson JR, Machado RD, Morgan NV, Atkinson C, et al. (2001) Clinical and molecular genetic features of pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia. N Engl J Med 345: 325-334.

33. Shintani M, Yagi H, Nakayama T, Saji T, Matsuoka R (2009) A new nonsense mutation of SMAD8 associated with pulmonary arterial hypertension. J Med Genet 46: 331-337.

34. Marin-Garcia J (2007) Systemic and pulmonary hypertension: Post-Genomic Cardiology. Academic Press.

35. Machado RD, Eickelberg O, Elliott CG, Geraci MW, Hanaoka M, et al. (2009) Genetics and genomics of pulmonary arterial hypertension. J Am Coll Cardiol 54: S32-S42.

36. Koehler R, Grunig E, Pauciulo MW, Hoeper MM, Olschewski H, et al. (2004) Low frequency of BMPR2 mutations in a German cohort of patients with sporadic idiopathic pulmonary arterial hypertension. J Med Genet 41: e127.

37. Sztrymf B, Coulet F, Girerd B, Yaici A, Jais X, et al. (2008) Clinical outcomes of pulmonary arterial hypertension in carriers of BMPR2 mutation. Am J Respir Crit Care Med 177: 1377-1383.

38. Austin ED, Loyd JE, Phillips JA III (2009) Genetics of pulmonary arterial hypertension. Semin Respir Crit Care Med 30: 386-398.

39. Machado RD, Aldred MA, James V, Harrison RE, Patel B, et al. (2006) Mutations of the TGF-sbeta type II receptor BMPR2 in pulmonary arterial hypertension. Hum Mutat 27: 121-132.

40. Pfarr N, Szamalek-Hoegel J, Fischer C, Hinderhofer K, Nagel C, et al. (2011) Hemodynamic and clinical onset in patients with hereditary pulmonary arterial hypertension and BMPR2 mutations. Respir Res 12: 99.

41. Austin ED, Phillips JA, Cogan JD, Hamid R, Yu C, et al. (2009) Truncating and missense BMPR2 mutations differentially affect the severity of heritable pulmonary arterial hypertension. Respir Res 10: 87.

42. Hamid R, Cogan JD, Hedges LK, Austin E, Phillips JA 3rd, et al. (2009) Penetrance of pulmonary arterial hypertension is modulated by the expression of normal BMPR2 allele. Hum Mutat 30: 649-654.

43. West J, Cogan J, Geraci M, Robinson L, Newman J, et al. (2008) Gene expression in BMPR2 mutation carriers with and without evidence of pulmonary arterial hypertension suggests pathways relevant to disease penetrance. BMC Med Genomics 1: 45.

44. Loyd JE (2011) Pulmonary arterial hypertension: insights from genetic studies. Proc Am Thorac Soc 8: 154-157.

45. Austin ED, Cogan JD, West JD, Hedges LK, Hamid R (2009) Alterations in oestrogen metabolism: implications for higher penetrance of familial pulmonary arterial hypertension in females. Eur Respir J 34: 1093–1099.

46. Johnson JA, Hemnes AR, Lane K, Robinson L, Gladson S, et al. (2010) Olmesartan Does Not Treat Pulmonary Arterial Hypertension In BMPR2R899X Mice. Am J Respir Crit Care Med 181: A6326.

47. Roberts KE, McElroy JJ, Wong WP, Yen E, Widlitz A, et al. (2004) BMPR2 mutations in pulmonary arterial hypertension with congenital heart disease. Eur Respir J 24: 371-374.

48. Therrien J, Rambihar S, Newman B, Siminovitch K, Langleben D, et al. (2006) Eisenmenger syndrome and atrial septal defect: nature or nurture? Can J Cardiol 22: 1133-1136.

49. Aldred MA, Comhair SA, Varella-Garcia M, Asosingh K, Xu W, et al. (2010) Somatic chromosome abnormalities in the lungs of patients with pulmonary arterial hypertension. Am J Respir Crit Care Med. 182: 1153-1160.

50. Leuchte HH, El Nounou M, Tuerpe JC, Hartmann B, Baumgartner RA, et al. (2007) N-terminal pro-brain natriuretic peptide and renal insufficiency as predictors of mortality in pulmonary hypertension. Chest 131: 402-409.

51. Lammers AE, Hislop AA, Haworth SG (2009) Prognostic value of B-type natriuretic peptide in children with pulmonary hypertension. Int J Cardiol 135: 21-26.

52. van Albada ME, Loot FG, Fokkema R, Roofthooft MT, Berger RM (2008) Biological serum markers in the management of pediatric pulmonary arterial hypertension. Pediatr Res 63: 321-327.

53. Bernus A, Wagner BD, Accurso F, Doran A, Kaess H, et al. (2009) Brain natriuretic peptide levels in managing pediatric patients with pulmonary arterial hypertension. Chest 135: 745-751.

54. Schumann C, Lepper PM, Frank H, Schneiderbauer R, Wibmer T, et al. (2010) Circulating biomarkers of tissue remodelling in pulmonary hypertension. Biomarkers 15: 523-532.

55. Hansmann G, Plouffe BD, Hatch A, von Gise A, Sallmon H, et al. (2011) Design and validation of an endothelial progenitor cell capture chip and its application in patients with pulmonary arterial hypertension. J Mol Med 89: 971-983.

56. Diller GP, Dimopoulos K, Broberg CS, Kaya MG, Naghotra US, et al. (2006) Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: a combined retrospective and case-control study. Eur Heart J 27: 1737-1742.

57. Toshner M, Voswinckel R, Southwood M, Al-Lamki R, Howard LS, et al. (2009) Evidence of dysfunction of endothelial progenitors in pulmonary arterial hypertension. Am J Respir Crit Care Med 180: 780-787.

58. Warwick G, Thomas PS, Yates DH (2008) Biomarkers in pulmonary hypertension. Eur Respir J 32: 503-512.

59. Benza R, Biederman R, Murali S, Gupta H (2008) Role of cardiac magnetic resonance imaging in the management of patients with pulmonary arterial hypertension. J Am Coll Cardiol 52: 1683-1692.

60. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, et al. (2009) Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 34: 1219-1263.

61. Rosenzweig EB, Feinstein JA, Humpl T, Ivy DD (2009) Pulmonary arterial hypertension in children: Diagnostic work-up and challenges. Prog Pediatr Cardiol 27: 4-11.

62. Hirsch R, Bagby MC, Zussman ME (2011) Fenestrated ASD closure in a child with idiopathic pulmonary hypertension and exercise desaturation. Congenit Heart Dis 6: 162-166.

63. Ferdman DJ, Brady D, Rosenzweig EB (2011) Common atrium and pulmonary vascular disease. Pediatr Cardiol 32: 595-598.

64. Beghetti M, Tissot C (2010) Pulmonary hypertension in congenital shunts. Rev Esp Cardiol 63: 1179-1193.

65. Beghetti M, Galiè N, Bonnet D (2012) Can “inoperable” congenital heart defects become operable in patients with pulmonary arterial hypertension? Dream or reality? Congenit Heart Dis 7: 3-11.

66. Galiè N, Rubin L, Hoeper M, Jansa P, Al-Hiti H, et al. (2008) Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. Lancet 371: 2093-2100.

67. Dearani JA, Connolly HM, Martinez R, Fontanet H, Webb GD (2007) Caring for adults with congenital cardiac disease: successes and challenges for 2007 and beyond. Cardiol Young 17: 87-96.

68. McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, et al. (2004) Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 126: 14S-34S.

69. Barst R, Rosenzweig BE (2011) Pediatric Pulmonary Hypertension: Screening, Diagnosis and Assessment. In: Beghetti M, ed. Pediatric Pulmonary Hypertension. Munich: Elsevier: 113-129.

70. Dimopoulos K, Giannakoulas G, Wort SJ, Gatzoulis MA (2008) Pulmonary arterial hypertension in adults with congenital heart disease: distinct differences from other causes of pulmonary arterial hypertension and management implications. Curr Opin Cardiol 23: 545-554.

71. Henkens IR, Gan CT, van Wolferen SA, Hew M, Boonstra A, et al. (2008) ECG monitoring of treatment response in pulmonary arterial hypertension patients. Chest 134: 1250-1257.

72. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, et al. (2009) Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 30: 2493-2537.

73. Kittipovanonth M, Bellavia D, Chandrasekaran K, Villarraga HR, Abraham TP, et al. (2008) Doppler myocardial imaging for early detection of right ventricular dysfunction in patients with pulmonary hypertension. J Am Soc Echocardiogr 21: 1035-1041.

74. Stringham R, Shah NR (2010) Pulmonary arterial hypertension: an update on diagnosis and treatment. Am Fam Physician 82: 370-377.

75. Maceira AM, Prasad SK, Khan M, Pennell DJ (2006) Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance. Eur Heart J 27: 2879-2888.

76. Sarikouch S, Koerperich H, Boethig D, Peters B, Lotz J, et al. (2011) Reference values for atrial size and function in children and young adults by cardiac MR: a study of the German competence network congenital heart defects. J Magn Reson Imaging 33: 1028-1039.

77. Kovacs G, Reiter G, Reiter U, Rienmuller R, Peacock A, et al. (2008) The emerging role of magnetic resonance imaging in the diagnosis and management of pulmonary hypertension. Respiration 76: 458-470.

78. Barst RJ, Agnoletti G, Fraisse A, Baldassarre J, Wessel D, et al. (2010) Vasodilator testing with nitric oxide and/or oxygen in pediatric pulmonary hypertension. Pediatr Cardiol 31: 598-606.

79. Douwes JM, van Loon RL, Hoendermis ES, Vonk-Noordegraaf A, Roofthooft MT, et al. (2011) Acute pulmonary vasodilator response in paediatric and adult pulmonary arterial hypertension: occurrence and prognostic value when comparing three response criteria. Eur Heart J 32: 3137-3146.

80. Moller JH, Patton C, Varco RL, Lillehei CW (1991) Late results (30 to 35 years) after operative closure of isolated ventricular septal defect from 1954 to 1960. Am J Cardiol 68: 1491-1497.

81. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, Van Domburg R, Van Rijen EH, et al. (2004) Outcome of patients after surgical closure of ventricular septal defect at young age: longitudinal follow-up of 22-34 years. Eur Heart J 25: 1057-1062.

82. Lammers AE, Diller GP, Odendaal D, Tailor S, Derrick G, et al. (2011) Comparison of 6-min walk test distance and cardiopulmonary exercise test performance in children with pulmonary hypertension. Arch Dis Child 96: 141-147.

83. Barst RJ, Gibbs JS, Ghofrani HA, Hoeper MM, McLaughlin VV, et al. (2009) Updated evidence-based treatment algorithm in pulmonary arterial hypertension. J Am Coll Cardiol 54: S78-S84.

84. Oishi P, Datar S, Fineman J (2011) Pediatric pulmonary arterial hypertension: current and emerging therapeutic options. Expert Opin Pharmacother 12: 1845-1864.

85. Tissot C, Ivy DD, Beghetti M (2010) Medical therapy for pediatric pulmonary arterial hypertension. J Pediatr 157: 528-532.

86. Jia B, Zhang S, Chen Z, Li Z, Li X, et al. (1998) Plasma endothelin 1 concentrations in children with congenital heart defects. Minerva Pediatr 50: 99-103.

87. Gorenflo M, Bettendorf M, Brockmeier K, Ulmer HE (2000) Pulmonary vasoreactivity and vasoactive mediators in children with pulmonary hypertension. Z Kardiol 89: 1000-1008.

88. Adatia I, Haworth SG (1993) Circulating endothelin in children with congenital heart disease. Br Heart J 69: 233-236.

89. Komai H, Adatia I, Elliott MJ, de Leval MR, Haworth SG (1993) Increased plasma levels of endothelin-1 after cardiopulmonary bypass in patients with pulmonary hypertension and congenital heart disease J Thorac Cardiovasc Surg 106: 473-478.

90. Hiramatsu T, Imai Y, Takanashi Y, Hoshino S, Yashima M, et al. (1997) Time course of endothelin-1 and nitrate anion levels after cardiopulmonary bypass in congenital heart defects. Ann Thorac Surg 63: 648-652.

91. Schulze-Neick I, Li J, Reader JA, Shekerdemian L, Redington AN, et al. (2002) The endothelin antagonist BQ123 reduces pulmonary vascular resistance after surgical intervention for congenital heart disease J Thorac Cardiovasc Surg 124: 435-441.

92. Opitz CF, Ewert R, Kirch W, Pittrow D (2008) Inhibition of endothelin receptors in the treatment of pulmonary arterial hypertension: does selectivity matter? Eur Heart J 29: 1936-1948.

93. Beghetti M, Hoeper MM, Kiely DG, Carlsen J, Schwierin B, et al. (2008) Safety experience with bosentan in 146 children 2-11 years old with pulmonary arterial hypertension: results from the European Postmarketing Surveillance program. Pediatr Res 64: 200-204.

94. Beghetti M, Haworth SG, Bonnet D, Barst RJ, Acar P, et al. (2009) Pharmacokinetic and clinical profile of a novel formulation of bosentan in children with pulmonary arterial hypertension: the FUTURE-1 study. Br J Clin Pharmacol 68: 948-955.

95. Beghetti M (2009) Bosentan in pediatric patients with pulmonary arterial hypertension. Curr Vasc Pharmacol 7: 225-233.

96. Maiya S, Hislop AA, Flynn Y, Haworth SG (2006) Response to bosentan in children with pulmonary hypertension. Heart 92: 664-670.

97. Brun H, Thaulow E, Fredriksen PM, Holmstrom H (2007) Treatment of patients with Eisenmenger's syndrome with Bosentan. Cardiol Young 17: 288-294.

98. Gilbert N, Luther YC, Miera O, Nagdyman N, Ewert P, et al. (2005) Initial experience with bosentan (Tracleer) as treatment for pulmonary arterial hypertension (PAH) due to congenital heart disease in infants and young children. Z Kardiol 94: 570-574.

99. Apostolopoulou SC, Manginas A, Cokkinos DV, Rammos S (2007) Long-term oral bosentan treatment in patients with pulmonary arterial hypertension related to congenital heart disease: a 2-year study. Heart 93: 350-354.

100. van Loon RL, Hoendermis ES, Duffels MG, Vonk-Noordegraaf A, Mulder BJ, et al. (2007) Long-term effect of bosentan in adults versus children with pulmonary arterial hypertension associated with systemic-to-pulmonary shunt: does the beneficial effect persist? Am Heart J 154: 776-782.

101. Benza RL, Barst RJ, Galie N, Frost A, Girgis RE, et al. (2008) Sitaxsentan for the treatment of pulmonary arterial hypertension: a 1-year, prospective, open-label observation of outcome and survival. Chest 134: 775-782.

102. Galiè N, Olschewski H, Oudiz RJ, Torres F, Frost A, et al. (2008) Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, mult icenter, efficacy studies (ARIES) group. Circulation 117: 3010-3019.

103. Zuckerman WA, Leaderer D, Rowan CA, Mituniewicz JD, Rosenzweig EB (2011) Ambrisentan for pulmonary arterial hypertension due to congenital heart disease. Am J Cardiol 107: 1381-1385.

104. Wang C, Wang J, Zhao L, Wang Y, Liu J, et al. (2008) Sildenafil inhibits human pulmonary artery smooth muscle cell proliferation by decreasing capacitative Ca2+ entry. J Pharmacol Sci 108: 71-78.

105. Nagendran J, Archer SL, Soliman D, Gurtu V, Moudgil R, et al. (2007) Phosphodiesterase type 5 is highly expressed in the hypertrophied human right ventricle, and acute inhibition of phosphodiesterase type 5 improves contractility. Circulation 116: 238-248.

106. Ghofrani HA, Voswinckel R, Reichenberger F, Olschewski H, Haredza P, et al. (2004) Differences in hemodynamic and oxygenation responses to three different phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension: a randomized prospective study. J Am Coll Cardiol 44: 1488-1496.

107. Singh TP, Rohit M, Grover A, Malhotra S, Vijayvergiya R, et al. (2006) A randomized, placebo-controlled, double-blind, crossover study to evaluate the efficacy of oral sildenafil therapy in severe pulmonary artery hypertension. Am Heart J 151: 851.e1-5.

108. Humpl T, Reyes JT, Holtby H, Stephens D, Adatia I (2005) Beneficial effect of oral sildenafil therapy on childhood pulmonary arterial hypertension: twelve-month clinical trial of a single-drug, open-label, pilot study. Circulation 111: 3274-3280.

109. Franchi SM, Barreto AC, Cicero C, Castro CR, Ribeiro ZV, et al. (2010) [Two-year follow-up of pulmonary arterial hypertension patients treated with sildenafil]. Arq Bras Cardiol 94: 671-677.

110. Vida VL, Gaitan G, Quezada E, Barnoya J, Castaneda AR (2007) Low-dose oral sildenafil for patients with pulmonary hypertension: a cost-effective solution in countries with limited resources. Cardiol Young 17: 72-77.

111. Barst RJ, Ivy DD, Gaitan G, Szatmari A, Rudzinski A, et al. (2012) A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. Circulation. 125: 324-334.

112. Humpl T, Reyes JT, Erickson S, Armano R, Holtby H, et al (2011) Sildenafil therapy for neonatal and childhood pulmonary hypertensive vascular disease. Cardiol Young 21: 187-193.

113. Lee JE, Hillier SC, Knoderer CA (2008) Use of sildenafil to facilitate weaning from inhaled nitric oxide in children with pulmonary hypertension following surgery for congenital heart disease. J Intensive Care Med 23: 329-334.

114. Namachivayam P, Theilen U, Butt WW, Cooper SM, Penny DJ, et al. (2006) Sildenafil prevents rebound pulmonary hypertension after withdrawal of nitric oxide in children. Am J Respir Crit Care Med 174: 1042-1047.

115. Fraisse A, Butrous G, Taylor MB, Oakes M, Dilleen M, et al. (2011) Intravenous sildenafil for postoperative pulmonary hypertension in children with congenital heart disease. Intensive Care Med 37: 502-509.

116. Stocker C, Penny DJ, Brizard CP, Cochrane AD, Soto R, et al. (2003) Intravenous sildenafil and inhaled nitric oxide: a randomised trial in infants after cardiac surgery. Intensive Care Med 29: 1996-2003.

117. Schulze-Neick I, Hartenstein P, Li J, Stiller B, Nagdyman N, et al. (2003) Intravenous sildenafil is a potent pulmonary vasodilator in children with congenital heart disease. Circulation 108: II167-II173.

118. Takatsuki S, Calderbank M, Ivy DD (2012) Initial Experience With Tadalafil in Pediatric Pulmonary Arterial Hypertension. Pediatr Cardiol 33: 683-688.

119. Barst R (2010) How has epoprostenol changed the outcome for patients with pulmonary arterial hypertension? Int J Clin Pract Suppl: 23-32.

120. Levy M, Celermajer DS, Bourges-Petit E, Del Cerro MJ, Bajolle F, et al. (2011) Add-on therapy with subcutaneous treprostinil for refractory pediatric pulmonary hypertension. J Pediatr 158: 584-588.

121. Lammers AE, Hislop AA, Flynn Y, Haworth SG (2007) Epoprostenol treatment in children with severe pulmonary hypertension. Heart 93: 739-743.

122. Ivy DD, Doran AK, Smith KJ, Mallory GB Jr, Beghetti M, et al. (2008) Short- and long-term effects of inhaled iloprost therapy in children with pulmonary arterial hypertension. J Am Coll Cardiol 51: 161-169.

123. Limsuwan A, Wanitkul S, Khosithset A, Attanavanich S, Samankatiwat P (2008) Aerosolized iloprost for postoperative pulmonary hypertensive crisis in children with congenital heart disease. Int J Cardiol 129: 333-338.

124. Stamm J, Risbano M, Mathier M (2011) Overview of current therapeutic approaches for pulmonary hypertension. Pulm Circ 1: 138-159.

125. Berger RM, Bonnet D (2010) Treatment options for paediatric pulmonary arterial hypertension. Eur Respir Rev 19: 321-330.

126. Iversen K, Jensen AS, Jensen TV, Vejlstrup NG, Sondergaard L (2010) Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial. Eur Heart J 31: 1124-1131.

127. Burgess G, Hoogkamer H, Collings L, Dingemanse J (2008) Mutual pharmacokinetic interactions between steady-state bosentan and sildenafil. Eur J Clin Pharmacol 64: 43-50.

128. Hislop AA, Moledina S, Foster H, Schulze-Neick I, Haworth SG (2011) Long-term efficacy of bosentan in treatment of pulmonary arterial hypertension in children. Eur Respir J 38: 70-77.

129. Simonneau G, Torbicki A, Hoeper MM, Delcroix M, Karlócai K, et al. (2012) Selexipag, an oral, selective IP receptor agonist for the treatment of pulmonary arterial hypertension. Eur Respir J.

130. Schermuly RT, Janssen W, Weissmann N, Stasch JP, Grimminger F, et al. (2011) Riociguat for the treatment of pulmonary hypertension. Expert Opin Investig Drugs 20: 567-576.

131. Stenmark KR, Rabinovitch M (2010) Emerging therapies for the treatment of pulmonary hypertension. Pediatr Crit Care Med 11: S85-S90.

132. Hansmann G, Zamanian RT (2009) PPARgamma activation: a potential treatment for pulmonary hypertension. Sci Transl Med 1: 12ps14.

133. Sallmon H, Hansmann G (2011) New therapeutic concepts for children and adults with pulmonary arterial hypertension. DIVI 2: 106-111.

134. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, et al. (2009) ACCF/AHA 2009 expert consensus document on pulmonary hypertension. A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol 53: 1573-1619.

135. Minai OA, Gudavalli R, Mummadi S, Liu X, McCarthy K, et al. (2011) Heart Rate Recovery Predicts Clinical Worsening in Patients with Pulmonary Arterial Hypertension. Am J Respir Crit Care Med 185: 400-408.

136. Lammers AE, Diller GP, Odendaal D, Tailor S, Derrick G, et al. (2011) Comparison of 6-min walk test distance and cardiopulmonary exercise test performance in children with pulmonary hypertension. Arch Dis Child 96: 141-147.

137. Koestenberger M, Ravekes W, Everett AD, Stueger HP, Heinzl B, et al. (2009) Right ventricular function in infants, children and adolescents: reference values of the tricuspid annular plane systolic excursion (TAPSE) in 640 healthy patients and calculation of z score values. J Am Soc Echocardiogr 22: 715-719.

138. van Loon RL, Roofthooft MT, Delhaas T, van Osch-Gevers M, ten Harkel AD, et al. (2010) Outcome of pediatric patients with pulmonary arterial hypertension in the era of new medical therapies. Am J Cardiol 106: 117-124.

This article was originally published in a special issue, **Congenital Heart Disease-Recent Discoveries and Innovations** handled by Editor(s). Dr. Georg Hansmann, Children's Hospital Boston, USA; Dr. Matthias Sigler, Georg-August University Goettingen, Germany