REVIEW ARTICLE

Pulmonary Hypertension in Children: An Overview

Bibhuti B. Das

Introduction

Pulmonary hypertension (PH) is an angioproliferative pulmonary vasculopathy, characterized by loss of normal endothelial function, abnormal response of vascular smooth muscle cell to stimuli, and from the activation of multiple molecular pathways. Normal pulmonary artery (PA) pressure in children is 20/12 mmHg with a mean of 15 mmHg at sea level. PH is defined as a mean PA pressure of 25 mmHg at rest measured by right-heart catheterization with a normal pulmonary capillary wedge pressure (PWCP) = 15 mmHg and pulmonary vascular resistance (PVR) index of >3 Woods units x sq.m.(1) The pediatric cardiologist plays a critical role in the diagnosis and management of the child with PH.

Pathophysiology

In normal PA vasculature smooth muscle tone is balanced by natural homeostatic mechanisms governed by genes, vasodilators (prostacyclin and nitric oxide (NO) and vasoconstrictors (thromboxane A_2 and endothelin-1) which balance each other. (2) Transforming growth factor gene is one such gene that has long been implicated in tissue repair, connective tissue growth, control and production of cytokines, synthesis of endothelin, ion channel regulation and angiogenesis. In genetically susceptible individuals, when there is insult to pulmonary vasculature in the form of shear stress or stretch, all the components of the PA (endothelium, smooth muscle cells and fibroblasts) react excessively resulting in an imbalance between vasodilator and vasoconstrictor mediators, defect in potassium ion channel, and increased synthesis of inflammatory mediators, which result in vasoconstriction, thrombosis, and remodeling (distal extension of smooth muscle into small peripheral, normally non muscular pulmonary arteries).(3) Thus, PH is associated with conditions causing chronic vasoconstriction, thrombosis, or abnormalities of vessel function.

Causes of PH in Children

PH is classified according to the World Health Organization (WHO) revised criteria (2003) which reflects the underlying etiology to be the primary contributor to disease.(4) The major causes of PH in children are (1) persistent pulmonary hypertension of the newborn (PPHN); (2) pulmonary arterial hypertension secondary to congenital systemic-to-pulmonary vascular shunts; (3) pulmonary venous hypertension arising from left sided heart disease; (4) PH with major venous or capillary involvement; (4) PH arising from chronic lung disease associated with hypoxia; (6) PH associated with chronic thrombotic-embolic disease; and (7) miscellaneous disorders that are associated with extrinsic compression of the vasculature.

Clinical Presentation

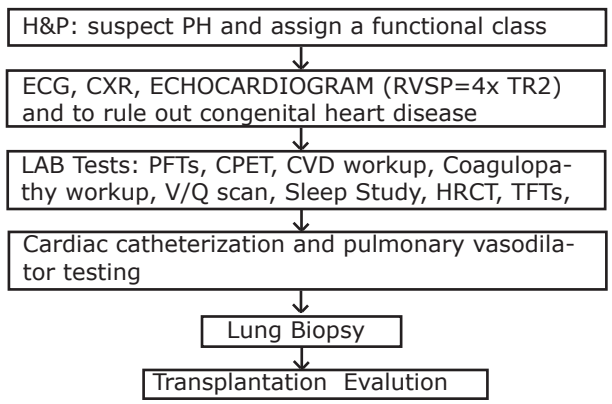
Children with PH may present with shortness of breath, exercise intolerance, and failure to thrive. They may experience chest pain, chronic cough, hemoptysis and recurrent syncope. Those with right-to-left shunting in the setting of elevated right-sided pressures may present with worsening cyanosis. Infants may present with irritability, poor feeding, or tachypnea. These findings are nonspecific and require careful evaluation before a diagnosis of PH can be established. The most important aspect of the clinical presentation is to assign the patient to a functional class (I to IV) according to the WHO Guidelines, which are a modification of the New York Heart Association (NYHA) heart failure classification.(5) This classification scale allows prognosis of long-term outcomes and provides treatment recommendations.

Diagnosis and Assessment

First step- History and physical examination: including onset and duration of symptoms, heart defect(s) and previous surgery, birth history including prematurity and chronic lung disease, sleep disorder, medications and toxins such as cocaine, methamphetamine, anorexigens, and a thorough family history to explore whether hereditary factors may contribute to their risk for the disease. Cardiac examination may reveal a right ventricular heave, palpable second heart sound, systolic murmur due to tricuspid regurgitation and a diastolic murmur of pulmonary insufficiency. The child with right heart failure may have increased jugular venous pressure, hepatomegaly, ascites, or pedal edema.

Second step- Cardiac non-invasive tests: Chest X-ray, ECG and echocardiography. Echocardiogram is the most commonly used modality to diagnose PH and right ventricular systemic pressure (RVSP) which is equivalent to PA pressure in the absence of significant pulmonary valve stenosis, is calculated by using Bernouli's equation (RVSP= 4 x tricuspid regurgitation jet velocity^2).

Third test - Additional laboratory tests are performed to rule out secondary forms of PH. A diagnostic work-up algorithm for children with PH is shown in figure-1.



PFT: pulmonary function tests, CPET: cardiopulmonary exercise testing, CVD: Collagen vascular disease, HRCT: high resolution CT, TFT: thyroid function tests

Fourth step- Most important is cardiac catheterization and testing for pulmonary vasoreactivity. Although non-invasive tests are useful in the evaluation of suspected PH, cardiac catheterization remains the "gold standard" for the diagnosis and severity of PH. Cardiac catheterization helps in the assessment and the selection of appropriate treatment.

Treatment

The pediatrician plays an important role in the care of children with PH. Annual influenza vaccination as well as pneumococcal vaccination is recommended unless there are contraindications. Patients should receive adequate antipyretic and antitussive medications during upper respiratory infections. However, decongestants with pseudoephedrine should be avoided as they may exacerbate PH. Diet and/or medical therapy should be used to prevent constipation, since the Valsalva maneuver transiently decreases venous return to the right side of the heart and may precipitate a syncopal episode.

The therapeutic approach to the child with PH begins with a thorough identification of the underlying cause(s) with treatment directed at the underlying cause.

These may include use of supplemental oxygen for patients with parenchymal lung disease, early surgical repair of cardiac defects, anti-inflammatory therapy for collagen vascular disease, continuous positive airway pressure therapy and adeno-tonsillectomy for patients with obstructive sleep apnea, and anticoagulation for chronic thromboembolic disease. Nearly all children with PH may need at least some "conventional therapy": oxygen, anticoagulants, digoxin, and diuretics. An overview of current approach and guidelines for treatment is shown in Figure 2

Therapy of PH is targeted against three well-characterized vascular changes: vasoconstriction, thrombus formation, and proliferation of smooth muscle or endothelial cells in the pulmonary vessels. Although, the principles of treatment of PH in children are often derived from observations in adults, data from adults are not easily extrapolated to children. Treatment of children with PH remains individualized based on the underlying etiology, functional class and vasoreactivity of pulmonary vasculature as determined by cardiac catheterization. Commonly used targeted PH therapy for children, their mechanism of action, dose/therapeutic range and side effects are described in table-1.

Figure-2: Current treatment strategies for children with PH

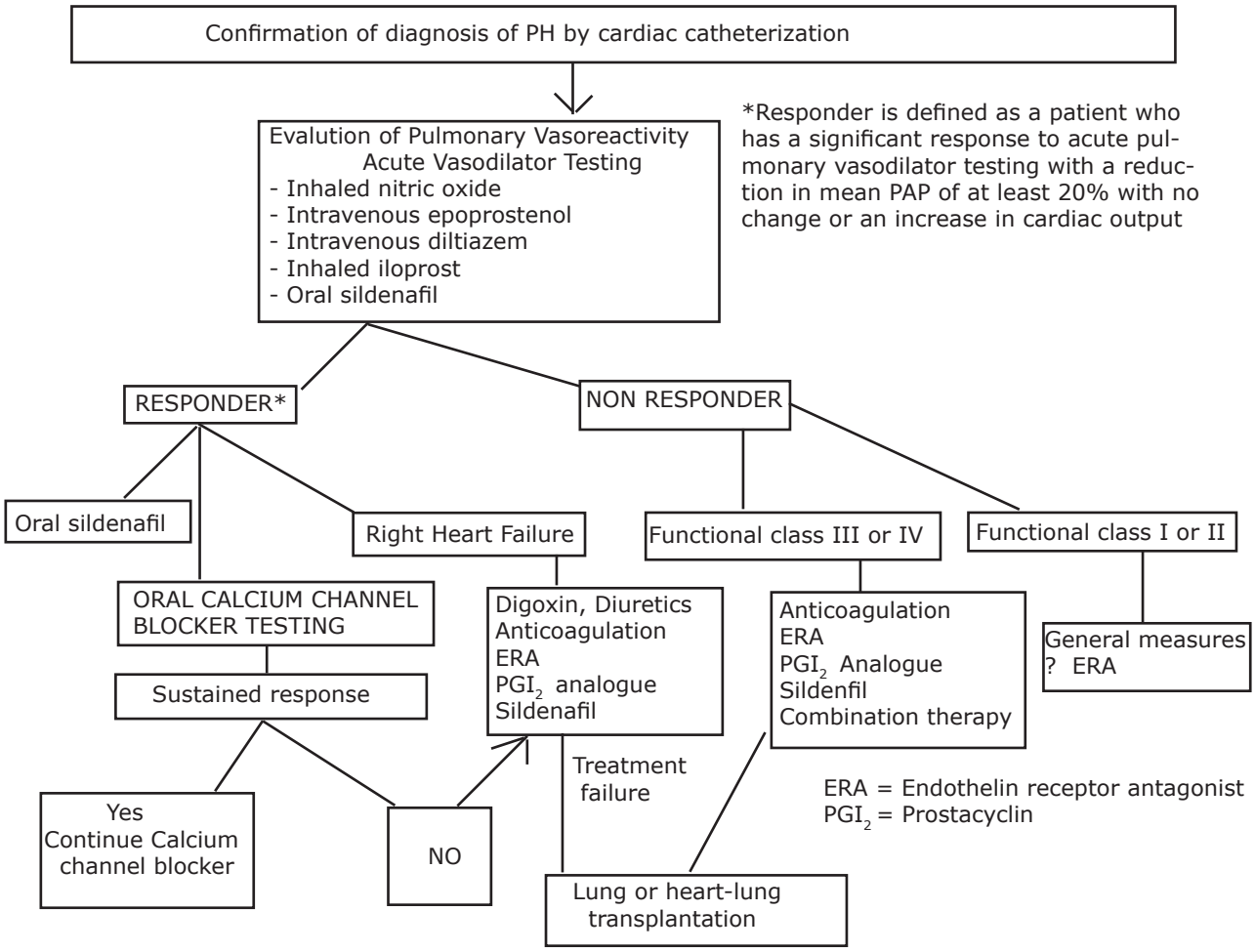


Table-1: Common targeted therapeutic agents for children with PH

Agent	Mechanism of action	Dose/ Therapeutic range	Side effects / Contraindication
Sildenafil	Phosphodiesterase inhibition, acts via eNOS -NO-cGMP pathway	0.5 mg/kg/dose up to 2mg/kg/dose PO every 4hr Titrate the dose to effect	Headache, flushing, nasal congestion, hypotension, diarrhea, dyspepsia. CI: hypersensitivity, pulmonary venoocclusive disease, patient taking nitrate in any form
Inhaled NO	Vasodilation, antiproliferation	Dose 5 ppm up to 20 ppm of NO, Titrated to effect	Rebound pulmonary hypertension, Methemoglobinemia
Bosentan	Endothelin receptor antagonist	Child (10-20 kg): 31.25 mg PO daily x 4 wks, then 31.25 mg PO BID, Child (20-40 kg): 31.25 mg PO BID x4 wks, then double the dose, Child > 40 kg: adult dose	Transaminase elevations/ hepatic toxicity; teratogenic, anemia. CI: Pregnancy, hypersensitivity
PGI_2 Analogue	Vasodilation Inhibition of platelets aggregation	IV: epoprostenol SQ:treprostinil Inhaled:iloprost (Dose: titrate to effect)	Headache, diarrhea, jaw, pain, leg pain, rash, nausea, flushing, syncope, catheter complication (IV)

CI: Contraindicated, PO: Per oral, NO: Nitric Oxide

Refractory PH

Despite advances in medical management of PH, patients are either non-responsive to such therapies or develop treatment-refractory disease. Patients, who often have marked symptoms of right heart failure or recurrent syncope, have limited treatment options. Atrial septostomy which facilitates right-to-left shunting can sometimes improve cardiac output and may contribute to improved survival for patients with refractory PH. (6) Atrial septostomy may also serve as a bridge to transplantation. Single or bilateral lung transplantation, as well as heart-lung transplantation, has been performed in patients with refractory PH. Results to date are highly variable, and the optimal transplantation procedure or patient selection criteria are yet to be established in children. (7) In practice, patients with medically refractory PH should be referred for evaluation at a lung transplantation center.

Summary

Recent advances in the understanding of molecular genetics, cell biology and pathophysiology, and treatment strategies have revolutionized the care of children with pulmonary hypertension, resulting in improved survival and quality of life for these patients. Because of the rarity of this disorder, children with PH merit evaluation and treatment at medical centers with experience in the medical, interventional, and surgical management of this disorder.

References

1. Rosenzweig EB, Barst RJ. Idiopathic pulmonary arterial hypertension in children. Current Opinion in Pediatrics. 2005, 17: 372
2. Farber HW, Loscalzo J. Pulmonary arterial hypertension. N Engl J Med. 2004; 351:1655
3. Newman JH, Trembath RC, Morse JA, et al. Genetic basis of pulmonary arterial hypertension: current understanding and future directions. J Am Coll Cardiol. 2004, 43: 33S
4. Simonneau G, Galie N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2004, 43, 5S
5. British Cardiac Society Guidelines and Medical Practice Committee. Recommendations on the management of pulmonary hypertension in clinical practice. Heart (British Cardiac Society) 2001, 86 (Suppl 1): II
6. Doyle RL, McCrory D, Channick RN, et al. Surgical treatments/interventions for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2002, 126: 63S
7. Mendeloff EN, Meyers BF, Sundt TM, et al. Lung transplantation for pulmonary vascular disease. Ann Thorac Surg. 2002, 73: 209

E-published: December 2008

FROM: Division of Pediatric Cardiology, Kochair Children's Hospital, University of Louisville, Louisville, USA

Address for Correspondence: Bibhuti B. Das, Division of Pediatric Cardiology, Kochair Children's Hospital, University of Louisville, Louisville, KY-40202, USA. E-mail: bdas99@hotmail.com