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EDITORIALS

Pulmonary Hypertension in Children – a Practical Approach

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ABSTRACT

Pulmonary hypertension (PH) is mean pulmonary arterial pressure above 25 mmHg at rest. Although considered a rare disease, the prevalence of PH in certain risk groups is higher, from 0.5% in patients with HIV infection to 30% in congenital heart disease (CHD) associating PH. In pulmonary arterial hypertension (PAH) associated with CHD, early changes of the vascular bed are reversible after correction of the defect, but there is a point from where the disease becomes irreversible or progression continues despite correction. Among patients with "operable" and "inoperable" CHD, there is a "gray area" group in between, which is defined by pulmonary vascular resistance equal to 4-8 WU/m and ratio of pulmonary vascular resistance to systemic vascular resistance of 0.3-0.5, measured by cardiac catheterization. In this situation a pulmonary vasoreactivity test is indicated. Pulmonary hypertension is a severe disease with increased morbidity and mortality. Pulmonary hypertension can result in death by decreased cardiac output, and heart failure.

Keywords: pulmonary hypertension, congenital heart disease, pulmonary vasoreactivity, nitric oxide administration

INTRODUCTION

Pulmonary hypertension (PH) is mean pulmonary arterial pressure above 25 mmHg at rest. The capillary pressure measurement helps differentiate between forms of precapillary PH (capillary pressure ≤15 mmHg) and postcapillary (capillary pressure >15 mmHg) which is relatively common in left heart disease and chronic obstructive pulmonary disease (1). The prevalence of pulmonary arterial hypertension (PAH) (or precapillary) of have been reported at 25-50 per million (2) and this form with all the subgroups is the most common in children. Regarding the prevalence of PH in children in Romania there is no data in medical literature, but there is a suspicion of a high prevalence associated with scarcity of cardiovascular surgery for children in the last decades. In the group of non operated CHD patients, it is reported that all patients with common arterial trunk, 50% of those with large ventricular septal defects (VSD) and 10-16% of those with large atrial septal defects (ASD) develop pulmonary hypertension (3). In the neonatal period the pulmonary hypertension was estimated around 0.2% in all neonates born at term. In this group it is thought that about 10% of the neonates with respiratory failure develop a degree of pulmonary hy-

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pertension (4), but invasive recent data shows a higher percentage (5). In other risk groups the prevalence of PH is higher. Thus, the prevalence of PH is 0.5% in HIV infected patients, 7-12% in patients with systemic sclerosis, and approximately 2 to 3.75% in patients with sickle cell anemia (4). PH in CHD was reported to 15.4% generally and 30% in non operated CHD (3,6). ❑

CLASSIFICATION

Current classification used in the PH in adults (Dana Point, 2008 with recent proposals for change, Nice, 2013) discusses five categories (Pulmonary Arterial Hypertension with Idiopathic, Heritable, Drug- and toxin-induced, Associated with Connective tissue diseases, or HIV infection, Portal hypertension, CHD, Schistosomiasis, Chronic haemolytic anaemia, Persistent pulmonary hypertension of the newborn subgroups, Pulmonary veno-occlusive disease then Pulmonary hypertension due to left heart diseases, Pulmonary hypertension due to lung diseases, Chronic thromboembolic pulmonary hypertension and PH with unclear multifactorial mechanisms) (7) (Table 1).

In pediatric patients the idiopathic PAH (8) and the arterial PH associated to CHD (9) (around 50% each) are commonly found, together with persistent pulmonary hypertension of the newborn. Although this classification is very broad, it was not considered optimal in pediatric pulmonary hypertension (10). Thus, in 2011, a more adequate classification of PH in children was established (11). In the new pediatric PH classification more importance is given to data related to premature birth, chromosomal abnormalities or other genetic abnormalities, congenital heart defects, breathing related sleep disorders, parenchymal disease secondary to chronic aspiration. Ten groups related to PH are identified in this classification (Table 1): prenatal or development pulmonary vascular hypertensive disease, perinatal pulmonary vascular maladaptation, pediatric cardiovascular disease, bronchopulmonary dysplasia, isolated pediatric pulmonary vascular hypertensive disease, multifactorial pediatric pulmonary vascular hypertensive disease associated with other birth defects, pediatric pulmonary diseases, pediatric thromboembolic disease, pediatric hypoxic-hypobaric exposure, pediatric pulmonary vascular disease associated with other systemic disorders (11).

There are many criteria in the functional anatomical classification which should be evaluated: type, size – with hemodynamic or anatomic evaluation, direction of the shunt, cardiac or extra-cardiac associated anomalies, and repair status.

Increased pressure in the pulmonary artery (either by overflow - congenital heart disease, or by intrinsic changes) is accompanied by endothelial dysfunction and vascular remodeling (smooth muscle cell proliferation, increased extracellular matrix, intravascular thrombosis). Following these changes, pulmonary vascular resistance increases. In CHD complicated by PAH, Eisenmenger syndrome is the next stage, meaning reversing of the shunt, which becomes right-to-left, with the advent of generalized cyanosis.

Extremely useful for framing the PH in CHD is the clinical classification proposed by Simonneau (7):

A. Eisenmenger syndrome:in large defects that led to a severe increase in pulmonary vascular resistance (PVR) with reversal of the shunt or bidirectional shunt;
B. PAH associated with systemic-to-pulmonary shunt: moderate-to-large defects, with mildly-moderate increased PVR; the shunt is dominantly systemic-to-pulmonar, without resting cyanosis;
C. PAH associated with smaller heart defects: small defects (usually ventricular septal defects less than 1 cm and atrial septal defects less than 2 cm - values considered to adulthood); clinical picture is close to idiopathic PAH;
D. PAH after corrective cardiac surgery. ❑

DIAGNOSIS AND MANAGEMENT

Diagnosis in PH must start by identifying symptoms commonly seen in this condition: exertional dyspnea, syncope, angina, reduced physical capacity. Special attention should be given to groups considered at risk for PH: connective tissue disease, HIV infection, use of appetite suppressant medications or other drugs, hemolytic anemia, portal hypertension. The diagnosis of PH can be raised in a routine echocardiographic assessment. The evaluation should include medical history, clinical evaluation, ECG, chest X-ray, routine biological samples and etiologic evaluation, transthoracic echocardiography, pulmonary functional tests.

Children	Adults
1. Prenatal or developmental pulmonary hypertensive vascular disease: • Associated with maternal or placental abnormalities • Associated with fetal pulmonary vascular maldevelopment • Associated with fetal cardiac maldevelopment (premature closure of foramen ovale or ductus arteriosus and CHD associated/causing pulmonary vascular disease in the fetus)	**1. Pulmonary arterial hypertension (PAH)** 1. Idiopatic 2. Heritable 3. Drug and toxin induced 4. Associated with • Connective tissue diseases • HIV infection • Portal hypertension • Congenital heart disease • Schistosomiasis • Chronic haemolytic anaemia 5. Persistent pulmonary hypertension of the newborn
2. Perinatal pulmonary vascular maladaptation (persistent pulmonary hypertension of the neonate) idiopathic or secondary to sepsis, CHD, trisomy, meconium aspiration, etc	**1′. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis**
3. Pediatric heart disease • Systemic –to-pulmonary shunts • Post-operative pulmonary arterial hypertension • Pulmonary vascular disease following staged palliation for single ventricle physiology • Pediatric pulmonary hypertensive vascular disease associated with congenital abnormalities of the pulmonary arteries/veins • Pulmonary venous hypertension	**2. Pulmonary hypertension due to left heart disease**
4. Bronchopulmonary dysplasia	**3. Pulmonary hypertension due to lung diseases and/or hypoxia**
5. Isolated pediatric pulmonary hypertensive vascular disease (isolated pediatric PAH)	**4. Chronic thromboembolic pulmonary hypertension**
6. Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes	**5. PH with unclear and/or multifactorial mechanisms** • Haematological disorders • Systemic disorders: sarcoidosis, histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis • Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders • Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis
7. Pediatric lung disease • Cystic fibrosis • Interstitial lung disease • Sleep disorders breathing • Chest wall and spinal deformities • Restrictive lung diseases • Chronic obstructive lung diseases	
8. Pediatric thromboembolic disease	
9. Pediatric hypobaric hypoxic exposure	
10. Pediatric pulmonary vascular disease associated with other system disorders • Pediatric portal hypertension • Pediatric haematological disorders • Pediatric oncological disease • Pediatric metaboli/endocrine disease: glycogen storage disease, Gaucher disease, thyroid disorders, mucopolysaccharidosis, etc. • Pediatric autoimmune or autoinflammatory disease • Pediatric infectious disease • Pediatric chronic renal failure	

TABLE 1. Comparative view regarding classification of pulmonary hypertension in children and adults (1,11).

Echocardiography is an extremely useful imaging test used in the diagnosis of pulmonary hypertension before catheterization to estimate pulmonary pressures (12). Based on tricuspid regurgitation jet (between right ventricle (RV) and right atrium (RA)) the pressure in the RV can be estimated, and in the absence of right ventricle outflow tract obstruction, right ventricular systolic pressure is considered equal to systolic pressure in the pulmonary artery. Systolic pulmonary arterial pressure of 36-50 mmHg, corresponding to a RV-RA gradient of 2.8-3.5 m/s can be attributed to a mild pulmonary hypertension. In this case, in symptomatic patients NYHA class II-III, a diagnostic cardiac catheterization is indicated (12).

If the patient is in NYHA class I, an echocardiographic reassessment is recommended at 6 months distance before cardiac catheterization recommendation. Echocardiography in congenital heart diseases allows the positive diagnosis. For children younger than 2 years with a left-to-right shunt (ASD, VSD or patent ductus arteriosus) the decision for surgery can be taken without a prior cardiac catheterization study for pulmonary resistance on the bases of normal peripheral saturation, presence of pulmonary overload (13). Echocardiography has proven reliable in certain pathologies like bronchopulmonary dysplasia associated with PAH (14).

For testing exercise capacity it is recommended the 6 minutes walking test (6MWT). This is an independent predictor of morbidity, mortality in heart failure, lung disease or idiopathic pulmonary hypertension (15). From the technical point of view, the 6MWT is a simple, inexpensive, reproducible with good standardization (1). It can be performed after the age of 5-6 years. However, there are medical opinions about its indication after the age of 7 years (15). It monitors: distance, the appearance of dyspnea on exertion (Borg scale) and oxygen saturation. Worse prognosis means a walking distance less than 332 meters or a walking distance less than 250 meters accompanied by O2 desaturation over 10%. Body weight, age, sex, height, patient motivation can influence the test. In children, it has similar diagnostic value with cardiopulmonary test (15).

For biochemical tests a prognostic value have the hyperuricemia and both basic and dynamic natriuretic peptide.

Right heart catheterization (RHC) is the "gold standard" in the diagnosis of pulmonary hypertension (16). To check the increment of lung resistance, the only method is the right heart catheterization which is invasive. In addition, the patients who might benefit from long-term treatment with calcium channel blockers (CCB) should be identified. For these it is indicated to test the pulmonary vasoreactivity. When performed in experienced centers, morbidity and mortality rates of RHC are low (1.1% and 0.05-0.2%) (17).

During RHC the following variables should be recorded: pulmonary artery pressure (PAP) (systolic, diastolic and mean), right atrial pressure, wedge pressure, and the pressure in the right ventricle (1). Sometimes left heart catheterization for recording left ventricular end-diastolic pressure it may be necessary. RHC is indicated in all patients to confirm the diagnosis of PH, to assess severity, and when taken in discussion the specific drug therapy (ESC Class I recommendation). The vasoreactivity testing in PH has several ESC indications (class I): patients with idiopathic, hereditary PAH, or associated to the use of appetite suppressant medications in order to identify patients who can be treated with high doses of CCB (1). Another indication for RHC and vasoreactivity testing is PAH related to CHD, for the patients being in the "gray" zone of operability.

A positive response to pulmonary vasoreactivity testing is defined as a reduction in mean pulmonary artery pressure $\geq$10 mmHg to reach an absolute value of the mean pulmonary artery pressure $\leq$ 40 mmHg with an oxygen content increased or unchanged (1).

Assessment of severity in PAH is extremely important regarding the decisions for treatment. Clinical evaluation is essential to assess the World Health Organization (WHO) functional class of PH. In patients with idiopathic or hereditary PAH without treatment, historical data showed a median survival period of six months in WHO class IV, of 2.5 years for WHO class III and of six years for WHO classes I and II (1). Other clinically evaluated factors of poor prognosis are age <14 years, reduced exercise capacity, syncope, haemoptysis, signs of right ventricular failure.

Treatment of PAH is complex and must be adapted to etiology and pulmonary vasoreactivity (18). It consists of general measures (birth control, moderate physical activity, prevention of infections, psychosocial therapy), supportive care (anticoagulation therapy - in the absence of contraindications, diuretic, digoxin, oxygen),

specific treatment (calcium channel blockers – reviewed at 3 month intervals, prostanoids, endothelin receptor antagonists, type 5 phosphodiesterase inhibitors).

Pulmonary hypertension is a severe disease. Pulmonary hypertension can result in death by decreased cardiac output, and heart failure (3). The average survival in idiopathic PAH is 2.8 years (3). For other forms of PH, the survival may vary depending on basic pathology.

A worse prognosis has PAH associated with collagen diseases. In PAH associated with CHD, the rate of progression of pulmonary vascular disease depends on the type and size of the anomaly and genetic predisposition (the population is heterogeneous). In this case, early changes are reversible after correction of the defect. Criteria for the definition of the 'operability' shall be based on performing a diagnostic cardiac catheterization, which shall reveal the pulmonary vascular resistance (PVR) <4 WU/m and the ratio of pulmonary resistance over systemic vascular resistance (PVR/SVR) <0.3. Corrective or palliative cardiac surgery should be performed before installation of associated PAH with increased pulmonary vascular resistance. Among patients with CHD there is a group found in the "gray area". This category is defined by RVP = 4-8 U/m and PVR/SVR = 0.3-0.5. In this situation, the next step is to test pulmonary vascular reactivity which involves inhalatory administration of pulmonary vasodilatative substances to study the magnitude of the vascular changes. After hyperoxia (FiO2 100%, five minutes) or 24 ppm nitric oxide (with FiO2 50%, for five minutes) a hemodynamic study is necessary. For this group if any of the following changes occur: a decrease in PVR with ≥20%, a decrease ratio of PVR/SVR with ≥20%, a final RVP <4 WU, a PVR/SVR <0.3, there is a chance of transforming inoperable into operable cases. In this case treatment with vasodilators such as endothelin receptor antagonists (bosentan) for 6-12 months is recommend, followed by a new cardiac catheterization that will determine if the resistances have migrated to the area of "operability". If vascular reactivity test is non responsive, the surgery is not recommended, and medical treatment for one year should continue (6, 19). There are studies that have documented the possibility of transition from the "gray zone" into the area of "operability". Corrective cardiac surgery in patients with pulmonary vascular resistance above a certain threshold increase risk of becoming persistent pulmonary hypertension after surgery and these patients have a worse long-term prognosis (20,21).

For cases of progressive deterioration interventional or surgical therapeutic methods exists for establishing intra- or extra-cardiac shunts (atrioseptostomy and Potts shunt). Those are designed to decompress pulmonary pressure when it reaches suprasystemic values. The last therapeutic method applied in PH is the lung or heart-lung transplantation. ❑

CONCLUSION

Pulmonary hypertension is a major disease with increases morbidity and mortality. A specific diagnostic protocol with clinical evaluation, 6 minutes walking test (if possible), echocardiography and right heart catheterization is necessary to assess the best therapy. Therapeutical management includes general measures, supportive care (anticoagulation therapy), specific treatment with calcium channels blockers, prostanoids, endothelin receptor antagonists, type 5 phosphodiesterase inhibitors. Interventional or surgical therapeutic procedures and transplant are regarded as end-therapy. Pulmonary hypertension can result in death by increasing pulmonary vascular resistance, decreased cardiac output, and heart failure.

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