Parameters for the Assessment of Pulmonary Vasodilator Therapy in Pulmonary Arterial Hypertension in Children

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Introduction: Pulmonary arterial hypertension (PAH) is a rare pathology with different etiologies, representing a cause of morbidity and mortality in the pediatric age group. Most cases of PAH in children are secondary to congenital heart diseases (CHD), followed closely by idiopathic PAH and familial forms. Our objective was to evaluate children with pulmonary arterial hypertension in order to establish which parameter is more useful for the assessment of pulmonary arterial hypertension.
Method: Twenty pediatric patients diagnosed with pulmonary arterial hypertension undergoing pulmonary vasodilator therapy were evaluated between March 2008 and January 2012 in the Pediatric Cardiology Department from Tirgu Mures County Emergency Clinical Hospital. Patients were assessed clinically, the exercise capacity was assessed using the 6-minute walk test, and echocardiography was performed. The initial assessment was considered at the time of initiation of the pulmonary vasodilator therapy, further evaluations being performed at intervals of 3 months.
Results: This study demonstrates the improvement of the functional class and 6-minute walk test, without compromising peripheral oxygen saturation whereas echocardiographic evaluation of patients did not show any echocardiographic parameter to correlate with improved exercise capacity and functional class.
Conclusion: The 6-minute walk test and NYHA functional class represent useful parameters for evaluating the efficiency of pulmonary vasodilator therapy

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Introduction

Pulmonary arterial hypertension (PAH) is a rare pathology, with different etiologies, representing a cause of morbidity and mortality in the pediatric age group. Most cases of PAH in children are secondary to congenital heart diseases (CHD), followed closely by idiopathic PAH and familial forms [1,2]. Despite different prognosis, the idiopathic and secondary PAH associated with CHD have similar lesions in the pulmonary circulation, characterized by vascular proliferation and remodeling of small pulmonary arteries: endothelial abnormalities, vasoconstriction, reduction of pulmonary arteriolar lumen, thrombosis, vascular proliferation, vascular remodeling, with consequently increased pulmonary artery pressure (PAP) and pulmonary vascular resistance (RPV), as well as appearance of right ventricular failure [3].

Enhanced knowledge about pathological changes of PAH, demonstrating the decreased production of endogenous pulmonary vasodilators (nitric oxide and prostacyclin) and increased synthesis of vasoconstrictors (endothelin and thromboxane A2), has conducted to the development of specific vasodilator therapy: inhibitors of phosphodiesterase-5, endothelin receptor antagonists, prostacyclin analogues [3,4,5].

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Early diagnosis and surgical treatment of CHD are essential in stopping the progression of pulmonary vascular lesions [6,7], the surgical treatment being potentially curative if it is performed prior to increase of pulmonary vascular resistance.

Prompt diagnosis and early initiation of target pulmonary vasodilator therapy represent common measures for management optimization of this progressive disease, regardless of the PAH etiology. Although there are differences in the therapeutic strategies of different etiological forms, the general recommendation is to initiate pulmonary vasodilator therapy with endothelin receptor antagonists, phosphodiesterase-5 inhibitors and prostacyclin analogues [6].

Assessment of patient prognosis represents the crucial element in the optimal management of PAH. Current guidelines suggest the following parameters with prognostic value in adults with PAH: functional class, the 6-minute walk test, biomarkers (BNP and NT-proBNP), echocardiographic and hemodynamic parameters [6]. These parameters are useful not only in establishing the initial prognosis of the patient, but also in assessing the therapeutic response to specific pulmonary vasodilator agents [8,9]. Pulmonary vasodilator therapy targets focus on improvement of symptoms, functional class, hemodynamic parameters, quality of life and survival [10]. Evaluation of therapeutic response is based on periodic evaluation of

these parameters. If there is an inadequate response, escalation therapy is recommended, i.e. association of a new therapeutic agent acting on another pathogenic pathway of PAH [6].

The 6-minute walk test is a standardized, reproducible test, which allows a quantitative assessment of the exercise capacity by determining the travelled distance, the dyspnoea on exercise, as well as the peripheral oxygen saturation, representsing an independent predictor factor of survival [11]. Current guidelines recommend the 6-minute walk test as a parameter of prognostic value [6]. The test is not usable under the age of 5–6 years.

A number of echocardiographic parameters correlate with the right heart hemodynamics, reflecting morphological and functional consequences of increased right ventricular afterload, and some of them were found to be prognostic indicators in PAH [12,13,15]. Current guidelines for the adult population estimated a favorable prognosis and a favorable response to pulmonary vasodilator therapy in the absence of pericardial effusion and a TAPSE value (tricuspid annular plane systolic excursion) over 20 mm [6,12,16]. Other echocardiographic parameters such as the right atrium area, the left ventricle eccentricity index, and the myocardial performance index of the right ventricle have prognostic value. An accurate estimate of prognosis involves the evaluation of several echocardiographic parameters [14].

Material and method

A study on a group of 20 pediatric patients diagnosed with PAH and receiving pulmonary vasodilator treatment was conducted between March 2008 and January 2012 in the Pediatric Cardiology Department from Tîrgu Mureș County Emergency Clinical Hospital. The diagnosis of PAH was confirmed by hemodynamic exploration, according to PAH definition as: mean pulmonary artery pressure ≥25 mmHg, wedge pulmonary capillary pressure <15 mmHg and normal or low cardiac output.

The age of patients included in the study group ranged from 6 to 16 years, with a mean age of 9.9 years (Figure 1); in terms of gender distribution, there was a slight predominance of females (55%).

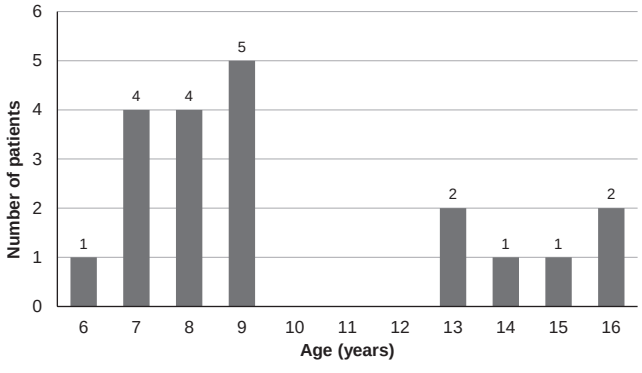

Fig. 1. Distribution of patients by age

In the assessment of PAH etiology for the patients under study there was a predominance of the secondary etiology, a total of 15 patients (75%) being diagnosed with PAH associated with CHD, while idiopathic PAH was present in 25% of the cases. Cardiac defects, which in the absence of surgical treatment were responsible for the appearance of PAH, were represented by: large ventricular septal defect (40%), common atrioventricular septal defect (10%), the extreme type of tetralogy of Fallot (10%), followed by persistent ductus arteriosus, univentricular heart and multiple peripheral pulmonary stenosis.

Evaluation of symptoms prior to initiation of pulmonary vasodilator treatment revealed a slight predominance of NYHA III functional class (55%), while the rest of the patients were classified as NYHA IV functional class.

All patients included in the study were administered specific pulmonary vasodilator therapy: endothelin receptor antagonists and phosphodiesterase-5 inhibitors, alone or combined therapy. 65% of patients (13 patients) were treated with only one pulmonary vasodilator agent, of which 10 patients were treated with endothelin receptor antagonists and 3 patients with phosphodiesterase-5 inhibitor, whereas 7 patients (35%), classified as NYHA IV functional class, followed a combined pulmonary vasodilator therapy.

Patients were assessed clinically as well as by echocardiography and the exercise capacity was assessed through the 6-minute walk test.

The initial assessment was considered at the time of initiation of the pulmonary vasodilator therapy, further evaluations being performed at intervals of 3 months. Classification into NYHA functional class was conducted in accordance with standard clinical criteria of the NYHA classification. The 6-minute walk test was performed according to standard procedures, with assessment of peripheral oxygen saturation before and after the test.

Echocardiographic estimation of systolic pulmonary artery pressure (PAPs) was performed through Doppler interrogation of the tricuspid regurgitation jet, using the simplified Bernoulli equation. Other echocardiographic parameters were: TAPSE, the myocardial performance index of the right ventricle – i.e. Tei index, right atrium area, the eccentricity index of the left ventricle, and presence of pericardial effusion.

Statistical analysis was performed using GraphPad Prism and Microsoft Excel, the Wilcoxon test, and the statistically significant level was set to a value of $p < 0.05$.

Results

NYHA functional class

Evaluation of the clinical status at 6 months after initiation of pulmonary vasodilator therapy demonstrated improvement of symptoms when compared to the initial assessment; most patients (60%) were classified as NYHA II functional class, while the remaining patients (40%) were classified as NYHA III functional class. After 6 months of