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RESEARCH ARTICLE

Epidemiological Characteristics and Prospective 6-Months Follow-up of Children with Pulmonary Arterial Hypertension

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Introduction: Pulmonary arterial hypertension (PAH) is a rare disease associated with significant morbidity and mortality. Pediatric patients often present with mixted aetiologies. **Objectives**: To characterize the epidemiology, management and outcome of pediatric PAH. **Methods**: Children with PAH were included and followed prospectively for six months. WHO functional class, 6-minute walk test, biomarkers, electrocardiogram, spirometers and echocardiographic parameters were evaluated in progressive PAH group. **Results**: Two hundred and four children were included in the study from July 2012 until July 2013, with a mean age of 6.13 years. Transient PAH patients (n=170, 83.33%) included newborns with persistent pulmonary hypertension (n=8, 3.92%) and children with congenital heart defects with systemic-to-pulmonary shunt-flow PAH (n=162, 79.41%) in whom PAH resolved after successful surgery correction. Progressive PAH (n=34, 16.66%) included patients with idiopathic PAH (n=5, 2.45%), Eisenmenger syndrome (n=17, 8.33%) and post-operative PAH (n= 6, 2.94%). Patients with progressive PAH remained stable in regards to clinical status, WHO functional class, 6-minute walk distance, biomarkers, spirometers parameters and echocardiographic parameters with prognostic value. **Conclusions**: Pediatric PAH is characterized by various age- specific diagnoses, the majority of which comprise transient forms of PAH. Pediatric PAH associated with congenital heart defects represents a heterogeneous group with highly variable clinical courses. PAH specific therapies may have contributed to disease stability and favorable outcomes.

Keywords: pulmonary arterial hypertension, children

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Pulmonary arterial hypertension (PAH) is a disease characterised by an increased pulmonary vascular resistance, progressing to advanced right heart failure and potentially leading to death. The diseases is associated with a 5-year mortality rate of approximatevely 25-60% [1] and the estimatated prevalence is 15-50 cases per million adults and 2-16 cases per million children [2-4].

The etiology of PHA in children differs from the one recorded at adult age, with a clear predominance of PAH associated with CHD [5,6].

Recent registries runed on pediatric population, such as the TOPP registry (Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension), on pediatric population, the U.S. REVEAL (Regystry to Evaluate Early and Long-Term PAH Disease management) Registry on children and adult population or a large registry from the nationwide Netherlands PH Service, for pediatric PH, identified new insights into the mechanisms os the disease progression, alowing predictions on the epidemiology, clinical practice and outcome of PAH in children [2-4, 6-7].

Pulmonary arterial hypertension with congenital heart disease (CHD) is the most commonly form diagnosed in childhood. The distinction between CHD with left-to-right shunts leading to advanced pulmonary vascular disease (PVD) in the context of the Eisenmenger syndrome, and the form of PHA without pulmonary vascular disease, is extremely important, as the latter group benefits the most from shunt closure, a procedure that can be performed nowadays on interventional or surgical route [1]. As a modification of the Dana Point classification, the Nice clinical classification of PH (pulmonary hypertension) futher highlights several aspects of pediatric disorders. being modified according to PAH associated with CHD [5].

Due to major advances in pulmonary vascular science, treatment strategies for PAH have been continuously evolving, aiming to improve survival rates and to accomplish a superior quality of life in childhood. The Nice pediatric PH treatment algorithm has been adapted according to the 2009 consensus adult PH treatment algorithm, adjusted in accordance to the specific of pediatric population and needs [5,8]. Major determinants of high risk in children with PAH include clinical evidence of right ventricular (RV) failure, the progression of symptoms, the presence of syncope, a World heart organization functional class III or IV, elevated or raising levels of B-type natriuretic peptide (BNP), a severe RV enlargement or dysfunction and the presenece of a significant pericardial effusion [9,10]. The treatment of choice in these cases is represented by an an endothelin receptor antagonist (bosentan) or a phosphodiesterase type- 5 inhibitor (PDE5) (sildenafil).

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The aim of this study was to investigate the epidemiological characteristics of pediatric PAH patients evaluated for a period of 1 year, between July 2013 and July 2014, in the Pediatric Cardiology Department from Tîrgu Mureşand to evaluate prospectively at 6 months the progressive PAH group in the current treatment era.

Methods

Study design

This prospective, non-interventional study was initiated in July 2013. Enrolled patients either had a known diagnosis of PAH before the beginning of the study or were diagnosed during the recruitment period, from July 2013 until January 2014. All enrolled patients were followed prospectively for 6 months.

Study patients

Patients aged between 1 day and 18 years were included in the study. The pediatric patients with PAH were classified in accordance with the evolutive forms of PAH. Transient forms of PAH were included in the first group (cases in which PAH is diagnosed long before development of severe PVD, including PPHN and PAH associated with CHD and a systemic-to-pulmonary shunt), while non-transient forms of PAH, including IPAH, PAH associated with CHD and advanced PVD- Eisenmenger syndrome or post-operative PAH, were assigned to the progressive PAH group.

Patients with PAH associated with CHD were categorized into four subgroups, depending on the left-to-right shunt anatomo- pathophysiology: pre-tricuspid shunt, post-tricuspid shunt, combined shunt, and complex CHD, including: atrioventricular defect, truncus arteriosus, single ventricle and abnormal development of the pulmonary vasculature.

In accordance with clinical classification of CHD associated with PAH, Nice 2013, the pediatric patients were categorized into: Eisenmenger syndrome, left-to-right shunts, PAH with co-incidental CHD and post-operative PAH.

A particular form of PAH associated with CHD includes the children with single ventricle physiology who have undergone bidirectional Glenn or Fontan-type procedures, this type not fulfilling the standard criteria for PAH.

Diagnosis of PAH

Diagnosis of PAH in transient forms was established using Doppler echocardiography, while the right heart catheterization (RHC) was performed in patients with progressive PAH following the European Society of Cardiology guidelines [11].

Study assessments of pediatric patients with PAH

In all patients we collected demographic data, including age, date at dagnosis, sex, weight and the presence of any syndromes (such as Down syndrome). The transient forms of PAH, that flow-PAH, were evaluated by echocardiography at 6 months after corrective surgery, and the infants with PPHN were evaluated by echocardiography at 1 month after birth. The progressive forms of PAH were evaluated at 6 months regarding clinical parameters: symptoms, WHO functional class, exercise capacity measured by the 6-minute walk test (6MWT), biomarkers- BNP, electrocardiography, spirometry, and echocardiography. By echocardiography we evaluated: 1/. the parameters that reflect the RV anatomy and physiology: RA area, tricuspid annulus diameter, pulmonary artery annulus diameter, left ventricle eccentricity index (LV EI), 2/. the echocardiographic parameters used to measure RV systolic and diastolic function: tricuspid annular plane systolic excursion (TAPSE), tricuspid annular velocity (S`), fractional area change (FAC), myocardial performance index (Tei), pericardial effusion, the pulsed wave Doppler interogation of the trans-tricuspid inflow, tissue Doppler,E/E` ratio, isovolumetric contraction time (IVCT), isovolumetric relaxation time (IVRT), and 3/. the echocardiographic parameters that reflect the hemodynamics: the tricuspid regurgitation velocity, the systolic pulmonary artery pressure (sPAP), the mean pulmonary artery pressure (mPAP), the acceleration time (ACT).

Statistical analysis

Statistical analysis was performed using SPSS software (Statistical Package for Social Sciences, 20 version, Chicago, IL, USA). Data were labeled as binary or quantitative nominal variables. Nominal variables were performed by frequency tables and chi-square statistical test was applied. The quantitative variables were tested using Kolmogorov-Smirnov test and were described as mean ± standard deviation, or median and percentile (25%, 75%). Differences between means or medians were analyzed using paired Student's t test or the Wilcoxon nonparametric test. The statistically significant level was set to a value of $p<0.05$. Due to the complexity of the pathophysiology of single ventricle, these patients were excluded from statistical analysis of echocardiographic parameters.

Results

1. Patients demographics and disease characteristics at inclusion

A total of 204 pediatric patients with PAH (59,8% women) were included with a median age of 6.13 years. They had the following diagnoses: transient PAH (n=170, 83.33%) and progressive PAH (n=34, 16.66%). Transient PAH included flow-PAH (n=162, 79.41%) and PPHN (n=8, 3.92%). All patients with flow-PAH had CHD with systemic-to-pulmonary shunts and the PAH resolved after surgery correction of CHD.Regarding PPHN, the echocardiographic evaluation at 1 month after birth showed no signs of PAH.Progressive PAH included IPAH (n=5, 2.45%), Eisenmenger syndrome (n=17, 8.33%) and post-operative PAH (n=6, 2.94%). In this subgroup also was

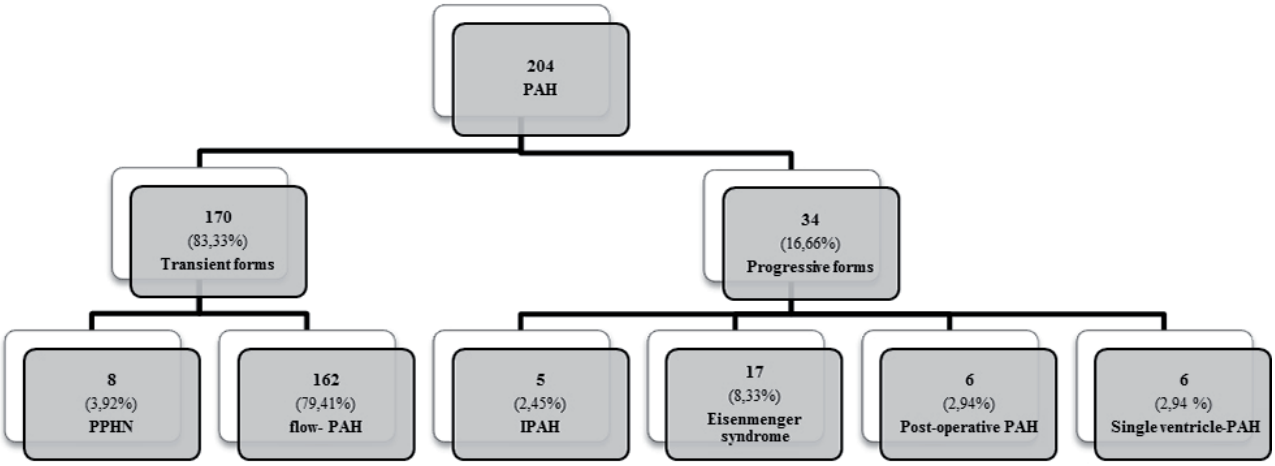

Fig. 1. Diagnosis of children with pulmonary arterial hypertension
Legend: PAH- pulmonary arterial hypertension, PPHN- persistent pulmonary hypertension of the newborn, IPAH- idiopathic pulmonary arterial hypertension

included the PAH associated with single ventricle physiopathology (n=6, 2.94%) (Figure 1).

Pacients with PAH associated with CHD (n=185, 90.68%) were categorized in according to the classification of CHD associated with PAH, Nice 2013: Eisenmenger syndrome (n=7, 8.33%), left-to-right shunts (n=162, 79.41%), and post-operative PAH (n=6, 2.94%) (Figure 2).

The anatomo-physiopathology classification of the left-to-right shuntconsisted of the evaluation of the: pre-tricuspid shunt,post-tricuspid shunt, combined shunt and complex CHD. The pre-tricuspid shunt was met in flow-PAH (n=30, 16.21%), and the post-tricuspid shunt (n=92%, 49.72) was responsible for the development of the flow-PAH in 83 patients (44.86%),for the evolution towardsEisenmneger syndrome in 7 patients (3.74%) and post-operative PAH (n=2, 1.08%). The combined shunt (n=24, 12.97%) was met in flow-PAH (n=21, 11.35%) and in post-operative PAH (n=2, 1.08%). The complex CHD were diagnosed in cases of 28 pediatric patients (n=15.13%) with flow-PAH, in cases of 9 patients (4.86%)

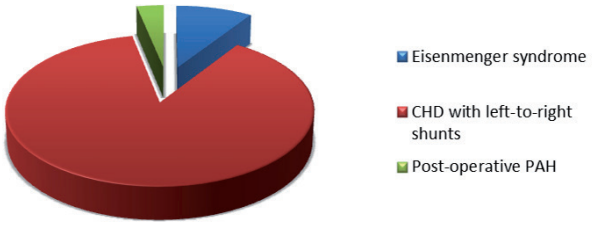

Fig. 2. Classification of pulmonary arterial hypertension associated with congenital heart disease
Legend: PAH: pulmonary arterial hypertension, CHD: congenital heart disease

with Eisenmenger syndrome and in 2 patients (1.08%) with post-operative PAH(Figure 3).

Genetic defects. Genetic syndromes, including Down syndrome, were present in 16.17% (n=33) of all PAH patients, of which 27 patients (13.23%) were diagnosed with flow-PAH and 6 patients (2.94%) with Eisenmenger syndrome.

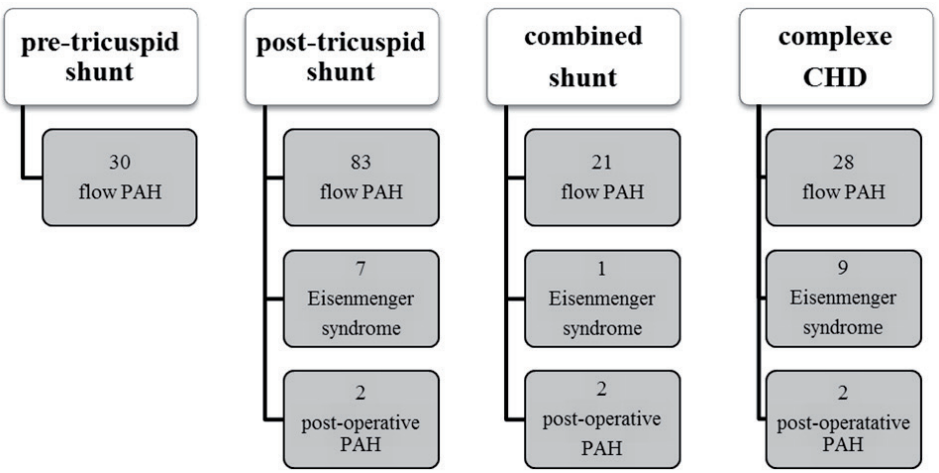

Fig. 3. Anatomo-pathophysiology classification of the left-to-right shunt
Legend: PAH- pulmonary arterial hypertension, CHD- congenital heart disease

2. Prospective 6-months follow-up of children with progressive pulmonary arterial hypertension

Pulmonary arterial hypertension- specific treatment consisted in administration of Sildenafiland Bosentan in monotherapy or combined therapy. Monotherapy with Sildenafil (n=3) or Bosentan (n=12) was the most frequently prescribed in patients with Eisenmenger syndrome, while bytherapy was the most frequently prescribed in IPAH (n=4).

Clinical simptoms, WHO functional class, exercise capacity measured by the 6MWT, BNP, electrogardiographic, spirometric and echocardiographic parameters were determined at inclusion and after6-months.

Clinical symptoms. The most common clinical symptoms reported were: dyspnea, fatigue, cyanosis, bone pain, weight deficit, hyperviscosity syndrome and signs of congestive heart failure, consisting of hepatomegaly and edema. Clinical assessment at 6 months of patients with progressive PAH hasnot demonstrated significant changesin terms of clinical symptomatology.

Functional class. In the case of 28 patients with progressive PAH the evaluation of FC at the initiation of the study revealed the predominance ofFC II (n=17, 60.7%), followed by FC III (n=10, 35.7%). No statistically significant changes were found in the evaluation of FC at 6 months, the patients with progressive PAH maintaining the FC II (p=0.51, 48%) and FC III (p=0.62, 48%). The evaluation of FC based on the etiology of PAH revealed the prevalence of FC II in patients with Eisenmenger syndrome (n=10, 58.8%), followed bythe post-operative PAH (n=5, 83.3%). Regarding IPAH, 40% of patients (n=2) were initially in FC II, 40% of patients (n=2) were in FC III, and 1 patient was in FC IV. At 6 months after initiation of the study it is found that the patients with post-operative PAH remain in the same FC, however, in the case of one patient with IPAH and 3 patients with Eisenmenger syndrome the FC was emphasized(Table I), (Figure 4).

Exercise capacity. The 6MWT was performed in patients with progressive PAH over 5 years, after 6 months at baseline there wasnot a significant improvement of the walk distance at 6MWT (p=0.44)(Figure 5).

Biomarkers. The evaluation of the serum level of the BNP at baseline and after 6 months revealed a statistically insignificant increase(p=0.82). The maximum level of BNP was determined in a patient with IPAH, in FC IV (3021pg/ml) (Table II).

Electrocardiographic parameters. The evaluation of the ECG initially and during the study did not reveal the presence of the cardiac arrhythmias (p=0,42), however, with regard to conduction abnormalities there was found a significant increase in the incidence of atrioventricular block of varying degrees (p=0.02).

Table I. Evaluation of functional class at baseline and after 6-months in progressive PAH subgroup

	FC at baseline		FCat 6-months		p value
	Frequency	Percentage	Frequency	Percentage	
FC II	17	60,7	12	48,0	0.51
FC III	10	35,7	12	48,0	0.62
FC IV	1	3,6	1	4,0	0.51
Total	28	100,0	25	100,0	

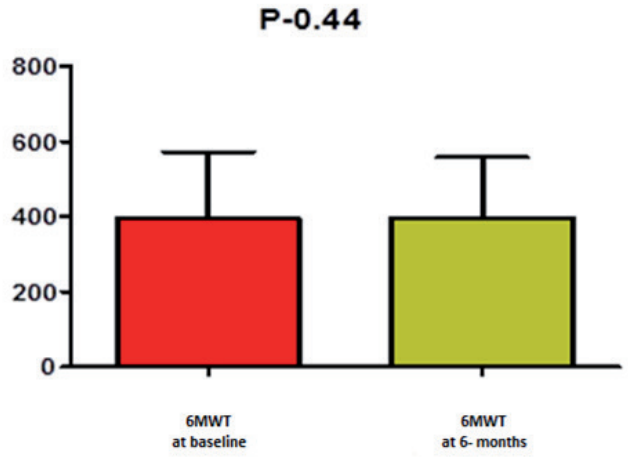

Fig. 5. Evaluation of the 6-minute walk test at baseline and after 6-months in progressive PAH subgroup
Legend: 6MWT: 6- minute walk test

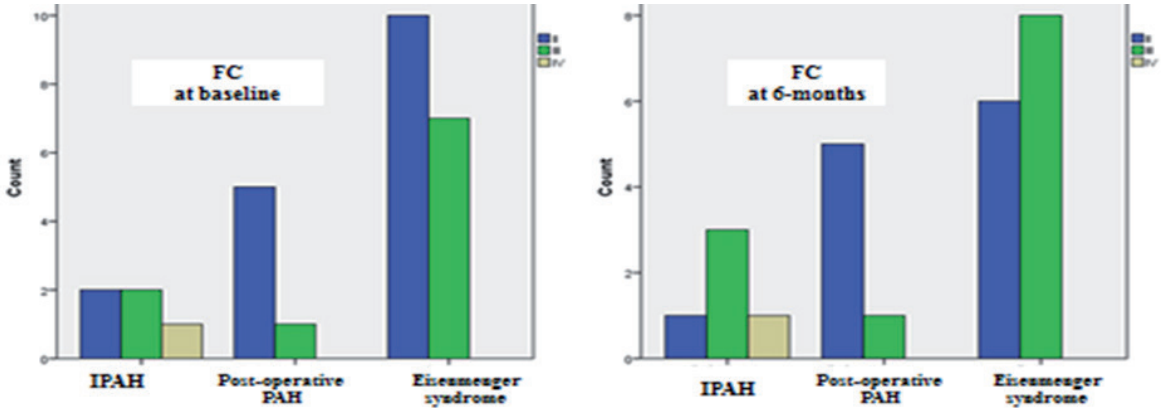

Fig. 4. Evaluation of functional class at baseline and after 6-months in progressive PAH subgroup
Legend: FC: functional class, IPAH: idiopathic pulmonary arterial hypertension, PAH: pulmonary arterial hypertension

Spirometry. In the case of 18 patients with progressive PAH the spirometry was performed at baseline and after 6 months.The forced vital capacity (FVC) significantly improved from baseline (p=0.05, CI 95%) (Figure 6).

Echocardiography. The evaluation at 6 months ofechocardiographic parameters who reflect the RV anatomy and physiology (RA area, tricuspid annulus diameter, pulmonary artery annulus diameter, LV EI) found a significant statistically increase in pulmonary artery diameter from baseline (p=0.03)(Figure7) (Table III).The echocardiographic parameters reflecting RV function (TAPSE, S`, FAC, Tei, pericardial effusion, E/E` ratio, IVCT, IVRT) did not change from baseline (Table III).The echocardiographic evaluation of hemodynamics was to determine the tricuspid regurgitation velocity, sPAP, mPAP andACT. The echocardiography at 6 months revealed a significant statistically increase of sPAP (p=0.02, CI:95%)(Figure 8) (Table III).

DISCUSSIONS

Pulmonary arterial hypertension can be diagnosed at any age, from the age of newborn to the adult. The distribution of etiology inpediatric PAH is different from that found in the adult population, with predominance of IPAH and PAH associated with CHD [3,6,7]. In the adult population the most frequent etiology of PAH is represented by connective tissue diseases [12]. The first objective of this study was to describe the epidemiological characteristics of pediatric PAH. Over 80% of patients with PAH evaluated during the course of the study presented transient forms of PAH, including flow PAH (79.41%) and PPHN (4%). The progressive forms (16.6%) were predominantly represented by Eisenmenger syndrome followed, in approximately equal percentages, by IPAH and post-operative PAH.

Pulmonary arterial hypertension associated with CHD is characterized by a wide spectrum of cardiac lesions with specific hemodynamic profile, which leads to heterogeneity of this group of patients. Using evaluation of anatomo-pathophysiology of left-to-right shunt, our study revealed the predominance of a post-tricuspid shunt in 55% of all patients with PAH associated with CHD, while cardiac lesions were represented by ventricular septal defect, patent ductus arteriosus and aorto-pulmonary defect. Complex CHD represented by atrioventricular defect, truncus arteriosus, CHD with pathophysiology of single ventricle,

Table II. Evaluation of the bone natriuretic peptide at baseline and after 6-months in progressive PAH subgroup

	BNP at baseline	BNP at 6-months
Number of values	27	13
Minimum	10.00	10.00
25% Percentile	17.70	14.60
Median	31.20	39.00
75% Percentile	92.50	80.50
Maximum	3021	275.0

Legend: BNP: bone natriuretic peptide

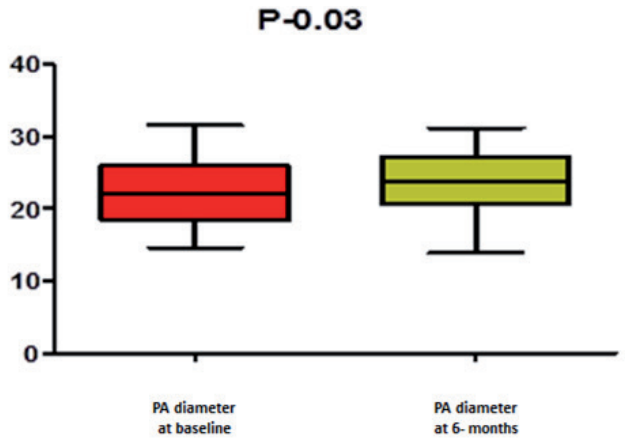

Fig. 7. Evaluation of pulmonary artery annulus diameter at baseline and after 6-months in progressive PAH subgroup
Legend: PA: pulmonary artery

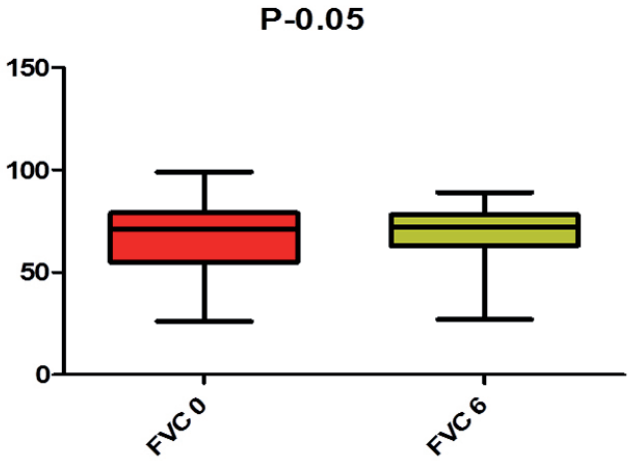

Fig. 6. Evaluation of forced vital capacity by spirometry at baseline and after 6-months in progressive PAH subgroup
Legend: FCV: forced vital capacity

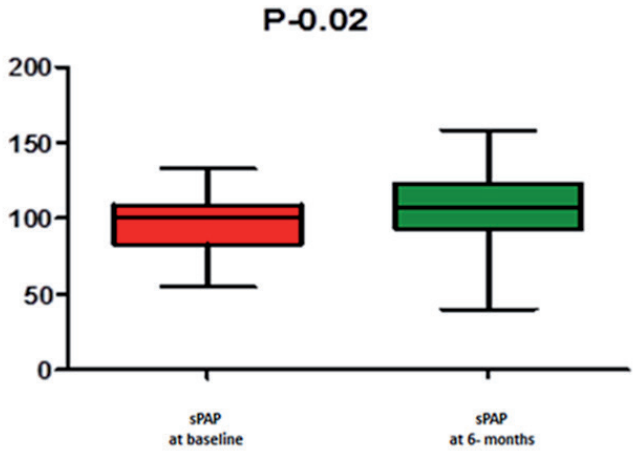

Fig. 8. The echocardiographic estimation of systolic pulmonary artery pressure at baseline and after 6-months in progressive PAH subgroup
Legend: sPAP: systolic pulmonary artery pressure

Table III. The echocardiographic parameters at baseline and after 6-months in progressive PAH subgroup

		Paired Differences					Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		
					Lower	Upper	
Pair 1	TRv 0 - TRv 6	-15,750	43,871	8,955	-34,275	2,775	0,092
Pair 2	sPAP 0 - sPAP 6	-8,000	16,092	3,285	-14,795	-1,205	0,023
Pair 3	mPAP 0 - mPAP 6	-3,773	12,313	2,625	-9,232	1,687	0,165
Pair 4	ACT 0 - ACT 6	-2,318	12,053	2,570	-7,662	3,026	0,377
Pair 5	LV EI 0 – LV EI 6	-,08458	0,49965	0,10199	-,29557	,12640	0,415
Pair 6	RA area 0 – RA area 6	-0,61696	3,45745	0,72093	-2,11207	0,87816	0,401
Pair 7	TAPSE 0 - TAPSE 6	-0,1458	3,8907	0,7942	-1,7887	1,4971	0,856
Pair 8	FAC 0 - FAC 6	0,304	11,198	2,335	-4,538	5,147	0,897
Pair 9	S` 0 – S` 6	-0,25667	2,48644	0,50754	-1,30660	0,79327	0,618
Pair 10	E/E` 0 - E/E` 6	0,004130	0,023868	0,004977	-,006191	0,014452	0,415
Pair 11	IVCT 0 - IVCT 6	5,708	18,224	3,720	-1,987	13,404	0,139
Pair 12	IVRT 0 - IVRT 6	-0,917	24,830	5,068	-11,401	9,568	0,858
Pair 13	Tei 0 - Tei 6	0,02682	0,32230	0,06872	-,11608	0,16972	0,700
Pair 14	Tr annulus 0 – Tr annulus 6	0,4208	2,2248	0,4541	-,5186	1,3603	0,364
Pair 15	PA annulus 0 PA annulus 6	-0,7636	1,5634	0,3333	-1,4568	-0,0704	0,032

Legend: TRv: the tricuspid regurgitation velocity, sPAP: the systolic pulmonary artery pressure, mPAP: the mean pulmonary artery pressure, ACT: the acceleration time, LV EI: the left ventricle eccentricity index, RA area: right atrial area, TAPSE: tricuspid annular plane systolic excursion, FAC: fractional area change, S`: tricuspid annular velocity, E/E`: E wave/E` wave ratio, IVCT: isovolumetric contraction time, IVRT: isovolumetric relaxation time, Tei: myocardial performance index, Tr annulus: tricuspid annulus diameter, PA annulus: pulmonary artery diameter.

CHD with abnormal development of the pulmonary circulation, followed by combined shunt were responsible for evolution to PAH in 21% and, respectively, 12,9% of cases.

The recent TOPP registry identified important clinical features specific for pediatric population with PAH. From the total of 362 children studied, 317 had PAH, out of which 182 (57%) were idiopathic or familial and 135 (43%) were associated with other disorders (in 115 cases being associated with a CHD) [1,7]. Another large registry for pediatric PAH in the Netherlands indicated that 2.845 of 3.263 pediatric patients with PH had PAH in different forms: transient PAH in 82% of cases and progressive PAH in 5%. In the group with progressive PAH, the form associated with CHD represented 72% of the studied population [4,5].

In the same time, the current study revealed a relatively high incidence of Down syndrome (n=33, 16.17%), a syndrome that was encountered as the most frequent chrosomal disorder (12%) in the registry runned in the Netherlands, similarly to the rate observed in the TOPP registry (13%) [4,5,7].

The prognosis of pediatric patients with progressive PAH improved significantly in the recent years, mainly due to the introduction of new therapeutic agents, used in children population after years of usage in adult population, which indicated good effects and low rates of adverse reaction [5,8].

Another objective of the current study was to assess prospectively at 6 months the parameters with prognostic value in cases of 34 pediatric patients with progressive PAH, who received specific pulmonary vasodilator treatment in monotherapy, Sildenafil or Bosentan, and bytherapy.

At baseline the most patients (60,7%) with progressive PAH presented with FC II, followed by FC III (35.7%), without significant changes regarding the FC evaluation at 6 months. Baseline FC is an important correlate and predictor of survival [13]. FC was repeatedly assesed during the follow-up, in order to obtain relevant data related to the severity of PAH and the response to therapy [14,15].

The 6MWT is widely used by clinicians as an integral component for assessing prognosis at baseline and treatment effect at follow-up. Initial studies have shown significant correlation between the baseline 6MWT and hemodynamic parameters, as well as survival [14,16]. However, several questions related to the 6MWT remained subject to debate, such as the distance that best correlates with exercise capacity and right heart function, and the critical value of this distance above which this can e considered as associated with an improved survival (>380 m, as suggested from Sitbon et al, or >440 m, as shown by the REVEAL registry) [17,18]. The current treatment goal for 6MWT is >380m, in current study the 6MW distance at baseline was 400 m, at 6 months patients maintaining their exercise capacity assessed by 6MWT (p=0,44).

The relevance of BNP has been demonstrated in outcome studies and as a secondary endpoint in some PAH treatment trials [14]. Recent data support the hypothesis that change in biomarkers levels carries prognostic information. The BNP value at 6 monthshas not changed significantly compared to thebaseline value, indicated goodresults in pediatric PAH patients in the current treatment era.

Evaluation of resting lung function was performed by spirometry. There was a significant improvement in FVC at 6 months (p=0.05) from the initiation of the study, which correlates with the symptoms of FC. Spirometry is useful in the diagnosis of patients with PAH, but the role of spirometry in the follow-up of patients with PAH is not yet well established.

Echocardiography is widely used as an initial diagnostic test to confirm the presence of PAH and it is used as a tool to provide prognostic information,especiallyregarding the echocardiographic assessment of RV function, which is the key determinant of outcome [14]. The Tei index, although it has been shown to be predictive of outcome, is largely dependent on loading conditions and on the degree of tricuspid regirgitation, wich limits its reliability [14,19,20]. TAPSE shown to be predictive of survival in patients with PAH-associated scleroderma [14,21].Right atrial and ventricular enlargement and the LV EI have also been shown to correlate with outcome among patients with IPAH [14,22]. The RA area at baseline seems to be one of the most robust echocardiographic determinants of outcome [22,23]. The presence of a pericardial effusion has been shown to be a strong predictor of mortality [24]. For patients in the study, the echocardiographic evaluation at 6 months showed no significant changes in parameters indicative of RV dysfunction.

The echocardiographic evaluation of right heart hemodynamics in patients with PAH evaluated during the study revealed a significant increase of sPAP (p=0,02), but there was not a significant change in other echocardiographic hemodynamic parameters, namely: mPAP, ACT. There is no consensus defining the severity of PAH as assessed by echocardiographic-derived parameters estimating RV systolic pressure. It is recommended that the interpretation of sPAP to be made in clinical context and according to other echocardiographic parameters reflecting RV pressure overload [25]. The current study, by monitoring echocardiographic parameters with prognostic value, demonstrated the effectiveness of specific therapy in patients with progressive PAH.

The limits of this study is the relatively small number of pediatric patients diagnosed with progressive PAH and the heterogeneity of the studied group.

Conclusions

The current study demonstrates that the most frequent forms of pediatric PAH are the transient types. The progressive forms of PAH are associated in most of cases with CHD, these patients representing a heterogeneous group with various presentations and disease courses.

The specific pulmonary vasodilator therapy has been shown to be effective and well tolerated by pediatric patients with progressive PAH.

Despite recent progress, pediatric PAH remains a devastating disease. The national and international registries play a key role in providing information that will improve understanding of the natural history, epidemiology and therapeutic response in order to optimize long-term outcomes in pediatric patients with PAH.

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