ORIGINAL RESEARCH

A Correlative Study of Spirometric Parameters and Markers of Right Ventricular Dysfunction in Pediatric Patients with Pulmonary Arterial Hypertension

Carmen Corina Șuteu[1], Iolanda Muntean[1], Cristina Blesneac[1], Brîndușa Căpîlna[2], Theodora Benedek[3], Rodica Togănel[1]

[1] Department M4, IIIrd Pediatric Discipline, University of Medicine and Pharmacy, Tîrgu Mureș, Romania
[2] Pediatric Clinic, County Emergency Clinical Hospital, Tîrgu Mureș, Romania
[3] Department M3, Clinic of Cardiology, University of Medicine and Pharmacy, Tîrgu Mureș, Romania

CORRESPONDENCE

Iolanda Muntean
Str. Gheorghe Marinescu nr. 50
540136 Tîrgu Mureș, Romania
Tel: +40 744 372 276
Fax: +40 265 210 505
E-mail: iolanda.muntean@gmail.com

Carmen Corina Șuteu • Str. Gheorghe Marinescu nr. 50, 540136 Tîrgu Mureș, Romania. Tel: +40 744 372 276, Fax: +40 265 210 505. E-mail: suteucarmen@yahoo.com

Cristina Blesneac • Str. Gheorghe Marinescu nr. 50, 540136 Tîrgu Mureș, Romania. Tel: +40 744 372 276, Fax: +40 265 210 505. E-mail: cristinablesneac@gmail.com

Brînduşa Căpîlna • Str. Gheorghe Marinescu nr. 50, 540136 Tîrgu Mureș, Romania. Tel: +40 265 212 111. E-mail: brindusarc@yahoo.com

Theodora Benedek • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551, E-mail: theodora.benedek@gmail.com

Rodica Togănel • Str. Gheorghe Marinescu nr. 50, 540136 Tîrgu Mureș, Romania. Tel: +40 744 372 276, Fax: +40 265 210 505. E-mail: rodicatoganel@yahoo.com

ABSTRACT

Background: Alteration in lung function is present in children with pulmonary arterial hypertension (PAH). We aimed to study the pulmonary function indices obtained by spirometry in pediatric patients with PAH, and to correlate them with B-type natriuretic peptide (BNP) and echocardiographic parameters. **Methods:** Thirty-one children with PAH were enrolled in this study, of those 26 patients (83.87%) associated shunt defect and 5 patients (16.12%) were diagnosed with idiopathic PAH. Forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FEV1/FVC, peak expiratory flow rate (PEFR), forced expiratory flow at 25–75% of the pulmonary volume (FEF 25–75) were evaluated by spirometry and correlated with BNP and echocardiographic parameters that reflect right ventricle function. **Results:** Restrictive pattern of pulmonary function was present in 51.6% (n = 16) of all PAH children. There were significant correlations between BNP with FVC (p = 0.001), FEV1 (p = 0.001), and FEV1/FVC (p = 0.001). Serum BNP level was significantly increased in the group of patients without shunt. Of those echocardiographic parameters that reflect right ventricle function, we found that TAPSE significantly correlated with PEFR (r = -0.47, p <0.01), and with FEF 25–75 (r = -0.39, p <0.01). **Conclusions:** Deterioration of the pulmonary function indices are correlated with BNP and echocardiographic parameters, markers of RV dysfunction. Being easy and reliable tests, pulmonary functions can be introduced among the follow-up tools in children with PAH.

Keywords: pulmonary function, pulmonary arterial hypertension, children

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a devastating and progressive disease characterised by vasoconstriction and vascular remodelling of the pulmonary arteries. PAH is currently defined by an mean pulmonary arterial pressure

(mPAP) ≥25 mmHg at rest as assessed by right heart catheterization (RHC), a pulmonary artery wedge pressure (PAWP) ≤15 mmHg, and a pulmonary vascular resistance (PVR) >3 Wood units in the absence of other causes of precapillary PH.[1]

Pulmonary function tests identify the contribution of underlying airway or parenchymal lung disease. Peacock AJ, considering the proximity of pulmonary vasculature and peripheral airways, postulated that it is possible that the latter may be affected either by the mechanical encroachment of enlarged vessels or by mediators of increased smooth muscle tone or proliferation.[2] In the context of impaired peripheral airways as a result of pathological mechanisms in the pulmonary vasculature, it is reasonable to postulate that pulmonary function might be affected by the development of PH.[3]

Assessment of lung function in children is considered an important diagnostic and prognostic tool regarding lung diseases.[4] Spirometry, the most readily available and useful pulmonary function test, measures the volume of air exhaled at specific time points during a forceful and complete exhalation after a maximal inhalation. The total exhaled volume, known as the forced vital capacity (FVC), the volume exhaled in the first second, known as the forced expiratory volume in one second (FEV1), and their ratio (FEV1/FVC) are the most important variables reported.

In the adult population with IPAH (idiopathic pulmonary arterial hypertension), previous studies of pulmonary function have been contradictory, with normal lung volumes, restrictive ventilator pattern, and airway obstruction.[3,5] Pulmonary function tests have not been well-studied in pediatric patients, especially in patients with PAH associated with congenital heart disease (CHD).

B-type natriuretic peptide (BNP), biomarker of right ventricle (RV) dysfunction, are inversely proportional with prognosis in PAH.[6] While in the adult pathology there are many data on the prognostic value of BNP serum level, in pediatric PAH the available data are limited, but few records suggest that BNP might be a useful marker in monitoring severity and treatment response assessment.[1,7] BNP can remain within the normal range despite profound cyanosis from suprasystemic PVR in patients with Eisenmenger syndrome (as long as right heart failure is not present).[6]

Transthoracic echocardiography, due to its noninvasive, safe and more affordable nature, is an important tool for PAH diagnosis and follow-up.[7] As long as RV performance is the key determinant of exercise capacity and long-term outcomes in patients with PAH, echocardiography remains a highly useful investigation in follow-up, providing quantitative and qualitative information on RV function with prognostic significance.[8]

The current study included the evaluation of the correlation of spirometric variables with markers of RV in pediatric patients with PAH.

MATERIALS AND METHODS

This is a prospective, noninterventional study assessing pulmonary function indices, the serum BNP level and echocardiographic parameters that reflect RV function in pediatric patients with PAH. Thirty-one children aged between 4 to 16 years, with a median age of 12 years, were evaluated between December 2013 and January 2015. PAH was defined in accordance with 2015 ESC/ERS Guidelines.[1] Patients with PAH were distributed into two groups: 1) patients with shunt defect – PAH associated with congenital heart defect (CHD) (group 1, n = 26) and 2) patients without shunt (IPAH) (group 2, n = 5).

Baseline assessment included the WHO (World Health Organization) functional class (FC) and the exercise capacity estimated with 6-minute walk test (6MWT) (in children ≥5 years). The 6MWT and was performed using standard protocol as ATS guidelines.[9]

Pulmonary assessment

Spirometry (nSpire 315000 Koko Legend Spirometer, Hertford, UK) was performed using standard technique measuring FEV1, FVC and FEV1/FVC, peak expiratory flow rate (PEFR), forced expiratory flow at 25–75% of the pulmonary volume (FEF 25–75). The measurement was taken before the echocardiographic examination and was performed using standard protocol as ATS guidelines.[10] The best trial was obtained from an average of three trials and the predictive values for age, sex, height and weight were calculated. Pulmonary functions obtained were classified as either normal, obstructed airways, restrictive or mixed patterns (Table 1).

Echocardiography

Conventional 2D and Doppler echocardiography in addition to tissue Doppler imaging were carried out for all pediatric patients with an IE33 equipment (Philips, Amsterdam, Netherlands). The echographic parameters that reflect RV function — tricuspid annular plane systolic excursion (TAPSE), tricuspid annular velocity (S`), fractional area change (FAC), myocardial performance index (Tei), and pericardial effusion were determined by echocardiography.

TABLE 1. Patterns of pulmonary function in pediatric patients with pulmonary arterial hypertension

Parameter	Normal	Obstruction	Restriction	Mixed
FVC	80% of predicted	Normal or slightly decreased (70 to 80% of predicted)	Severely decreased (<70% of predicted)	Decreased
FEV1/FVC	75–80% of predicted	Severely decreased (<60% of predicted)	Normal or increased (>85% of predicted)	Decreased
	n = 5 (16.1%)	n = 9 (29%)	n = 16 (51.6%)	n = 1 (3.2%)

FVC – forced vital capacity, FEV1 – forced expiratory volume in one second, FEV1/FVC – forced expiratory volume in one second/ forced vital capacity ratio, n – number

Measurement of serum BNP level

The serum samples were collected in each patient in close temporal proximity to the echocardiographic assessment. Serum BNP (range 0–100 pg/mL) was measured by an ARCHITECT i 1000SR Immunoassay Analyzer equipment (Abbott Diagnostics, Illinois, USA) in peripheral venous blood samples.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and the informed consent was taken from all parents before taking any data or doing any tests.

Statistical analysis

SPSS software (Statistical Package for Social Sciences, 20 version, Chicago, IL, USA) was applied for statistical analysis. 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 Mann-Whitney test. The statistically significant level was set to a value of $p < 0.05$.

RESULTS

The study included 31 children (13 girls – 41.9%, 18 boys – 58.06%), the median age was 12 years, and the average weight was 32.1 kg.

The result of pulmonary function tests of the studied patients are shown in Table 1. Restrictive pattern of functions was present in 51.6% (n = 16) of all PAH children, followed by obstructive pattern (n = 9.29%).

The correlation of BNP with the pulmonary function indices in the studied patients documented a significant association of BNP with FVC (p = 0.001), FEV1 (p = 0.001), and FEV1/FVC (p = 0.001) (Table 2).

When we studied the correlation between echocardiographic parameters that reflect RV function and the pulmonary function indices in all patients included in the study, we found that there was a significant correlation between TAPSE and PEFR (r = -0.47, p <0.01), and TAPSE and FEF 25–75 (r = -0.39, p <0.01) (Table 3).

Of the 31 pediatric patients with PAH included in the study, 26 patients (83.87%) associated shunt defect (group 1), and 5 patients (16.12%) were diagnosed with IPAH (group 2). In our study we could not find any significant differences in regard to the age, sex, and weight between group 1 and group 2, but there was a significant difference between these two groups regarding the length (p = 0.04) (Table 4).

We could not find any significant associations between the functional parameters in the two studied groups: functional class (p = 0.38) and 6MWT (p = 0.35), respectively (Table 4). There were no statistically significant differences between children with shunt defect and children without shunt defect regarding the results of pulmonary function tests (p >0.05) (Table 4). Serum BNP level was significantly increased in the group of patients without shunt (group 2) (p = 0.04) (Table 4).

Of the echocardiographic parameters that reflect RV function there was a significant difference between groups

TABLE 2. Correlation of pulmonary function indices with B-type natriuretic peptide

	FVC	FEV1	FEV1/FVC	PEFR	FEF 25–75
BNP	p = 0.001	p = 0.001	p = 0.001	p = 0.244	p = 0.123

FVC – forced vital capacity, FEV1 – forced expiratory volume in one second, FEV1/FVC – forced expiratory volume in one second/ forced vital capacity ratio, PEFR – peak expiratory flow rate, FEF 25–75 – forced expiratory flow at 25-75% of the pulmonary volume, BNP – B-type natriuretic peptide

TABLE 3. Correlation of pulmonary function indices with echocardiographic parameters that reflect right ventricular function

Echo parameters that reflect RV function	FVC	FEV1	FEV1/FVC	PEFR	FEF 25-75
TAPSE	r = -0.04	r = -0.15	r = -0.005	r = -0.47*	r = -0.39*
FAC	r = 0.11	r = 0.13	r = 0.32	r = 0.002	r = 0.09
Tei	r = -0.10	r = -0.07	r = 0.11	r = 0.06	r = 0.08
S`	r = -0.08	r = -0.20	r = -0.34	r = -0.26	r = -0.19
pericarditis	66.5 ± 9.9	67.3 ± 6.9	105.9 ± 4.8	56.1 ± 16.1	76.5 ± 16.8

FVC – forced vital capacity, FEV1 – forced expiratory volume in one second, FEV1/FVC – forced expiratory volume in one second/forced vital capacity ratio, PEFR – peak expiratory flow rate, FEF 25-75 – forced expiratory flow at 25-75% of the pulmonary volume, TAPSE – tricuspid annular plane systolic excursion, FAC – fractional area change, Tei – myocardial performance index of right ventricle, S` – tricuspid annular velocity
* – very significant correlation (p <0.01),
Pearson Correlation -r

in FAC (p = 0.04). Interestingly, no differences regarding TAPSE, Tei, S`, and pericardial effusion were found in the study groups.

DISCUSSION

Pulmonary function tests identify the contribution of underlying airway or parenchymal lung disease. The results of the study showed that pulmonary function tests are modified in pediatric patients with PAH. Leonard M *et al.* found that children with severe PAH associated with CHD presented significant reduction in FVC.[11] Our study confirmed that restrictive pattern is the most striking characteristic of pulmonary function test, followed by the obstructive pattern. These findings are in agreement with the study of Sabry AF *et al.*[4] The restrictive pattern, characterized by severely decreased FVC, is due to the lung stiffness and to the reduced lung compliance secondary to increased pul-

TABLE 4. Comparison of baseline clinical, functional, laboratory, pulmonary function indices and echocardiographic parameters characteristics between PAH pediatric groups

	All pediatric patients with PAH (n = 31)	Group 1 Shunt defect (n = 26)	Group 2 No shunt defect (n = 5)	p value
Age, yr	12 (4–16)	12.5 (4–16)	9 (6–12)	0.11**
Female gender	13 (41.9)	10 (38.5)	3 (60.0)	0.37#
Weight, kg	32.1 ± 13.9	33.1 ± 14.1	26.8 ± 7.4	0.33*
Length, cm	138 ± 20.1	140.2 ± 20.8	126.4 ± 10.5	0.04*
WHO FC II/III/IV	17/12/2	15/10/1	2/2/1	0.38#
6MWT distance, m	394.1 ± 12.39	403.1 ± 10.5	348.0 ± 18.3	0.35*
BNP, pg/ml	49.7 (4.2–192.5)	32.2 (4.2–180.7)	77.7 (15.8–192.5)	0.04**
FVC	67.8 ± 15.3	67.5 ± 16.1	69.4 ± 11.5	0.81*
FEV1	67.8 ± 14.9	66.7 ± 15.4	72.2 ± 8.2	0.45*
FEV1/FVC	106.5 ± 7.3	106.7 ± 7.6	105.8 ± 6.5	0.79*
PEFR	58.8 ± 16.2	58.3 ± 16.8	61.4 ± 13.5	0.70*
FEF 25-75	78.9 ± 26.2	77.7 ± 27.1	85.2 ± 21.9	0.56*
Echo parameters that reflect RV function				
TAPSE	18.9 ± 5.3	19.1 ± 5.3	17.9 ± 6.2	0.65*
FAC	36.2 ± 9.2	37.8 ± 8.6	28.8 ± 8.6	0.04*
Tei	0.65 ± 0.17	0.63 ± 0.17	0.73 ± 0.14	0.27*
S`	10.1 ± 2.6	10.1 ± 2.8	10.4 ± 2.1	0.72*
pericarditis	7 (23.3)	5 (20.0)	2 (40.0)	0.33#

PAH – pulmonary arterial hypertension, WHO FC – functional class, 6MWT – six minute walk test, BNP – B-type natriuretic peptide, FVC – forced vital capacity, FEV1 – forced expiratory volume in one second, FVC/FEV1 – forced vital capacity/forced expiratory volume in one second ratio, PEFR – peak expiratory flow rate, FEF 25-75 – forced expiratory flow at 25-75% of the pulmonary volume, TAPSE – tricuspid annular plane systolic excursion, FAC – fractional area change, Tei – myocardial performance index of right ventricle, S` – tricuspid annular velocity
*p value using Student's t-test; **p value using Mann Whitney test; #p value using Chi-square test

monary pressure. Abnormalities in endothelial function, including impaired production of prostacyclin and nitric oxide, and excessive synthesis of endothelin have well-known effects on the bronchial system.[3,12] Martin C *et al.*, examining the effect of the endothelin receptor antagonist bosentan on endothelin-induced bronchoconstriction, concluded that bosentan completely prevents ET-receptor agonist (IRL1620)-induced bronchoconstriction.[13] In the evolution of PAH patients, cardiac enlargement with its compressing effect and left ventricular dysfunction cause impaired respiratory muscle perfusion, which add an obstructed element.[4]

The ability to walk for a distance is an easy way to measure exercise capacity in patients with cardiac and pulmonary disease. Although some data are available, normative values of 6MWT for age, sex, and leg length have not been well standardized in children, and the predictive value of the 6MWT in pediatric PAH has not been proven.[6,14] In many centers the changes in 6MWT are used for longitudinal monitoring of patients. In our study and in another study done by Jing ZC *et al.* it was found that no functional parameters correlated well with pulmonary function indices.[3] Significant correlation between 6MWT and FEV1 has been shown in other studies involving patients with chronic pulmonary disease.[15]

Considering all PAH patients, the present study showed that FVC, FEV1, FEV1/FVC had very significant positive correlation with serum BNP level, marker of the RV dysfunction. Bernus A *et al.* found that BNP correlated with hemodynamic parameters, which have been shown to be predictive of outcomes in PAH, and are considered indicators for disease severity. In addition, they observed that a high BNP is indicative of poor survival, more so in IPAH patients.[16] Comparing the two studied groups, the current study could demonstrate significant differences regarding the BNP, elevated levels of BNP being revealed in pediatric patients with IPAH. The current study showed that pulmonary function indices are associated with RV dysfunction, which is more present in patients with IPAH.

As long as RV function is an important determinant of clinical status and outcomes in PAH, the assessment of RV function by echocardiography continues to play a central role in PAH diagnosis and follow-up.[6] Echocardiography can measure a number of RV parameters that have been shown to be key determinants in the prognosis of PAH, and which may be used as specific goals for treatment. Recently, TAPSE, alongside FC and NT-proBNP (N-terminal pro b-type natriuretic peptide), has been recognized as treatment goal in pediatric PAH.[8] The results in this study show that PEFR and FEF 25–75, indicating small airway

obstruction pattern, correlate with TAPSE. Some published studies have evaluated the correlation between spirometric parameters and pulmonary artery systolic pressure estimated by echocardiography.[18,19] However, from our knowledge, no study has evaluated the correlation of pulmonary function indices with echocardiographic parameters that reflect RV function, until now.

The main limitation of our present work is that it was an observational study with a small number of pediatric patients diagnosed with PAH. In addition, the studied group is heterogeneous.

CONCLUSION

The positive correlations of pulmonary function indices with BNP and with echocardiographic parameters that reflect RV function support the idea that resting lung function measurements can be introduced among the follow-up tools in children with PAH. The restrictive pattern was associated with most of the patients of the study, proving that lung compliance is affected in pediatric patients with PAH.

CONFLICT OF INTEREST

Nothing to declare.

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