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Doppler echocardiogram, oxygen saturation and submaximum capacity of exercise in patients with cystic fibrosis ☆

Paula Maria Eidt Rovedder [a,*], Bruna Ziegler [a], Lilian Rech Pasin [b], Greice Rampon [b], Antônio Fernando Furlan Pinotti [c], Paulo de Tarso Roth Dalcin [d], Sérgio Saldanha Menna-Barreto [d]

[a] *Serviço de Pneumologia of Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul (UFRGS), Brazil*
[b] *Faculdade de Medicina, UFRGS, Brazil*
[c] *Serviço de Cardiologia, Hospital de Clínicas de Porto Alegre (HCPA), Brazil*
[d] *Departamento de Medicina Interna, Faculdade de Medicina, UFRGS; Serviço de Pneumologia, HCPA, Brazil*

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Abstract

Study objectives: To determine the relationship between pulmonary arterial systolic pressure (PASP) and submaximum capacity of exercise, using the six-minute walk test (6MWT) in patients with cystic fibrosis (CF), and to investigate the relation between echocardiographic findings and results of 6MWT, clinical scores, chest radiograph scores and lung function tests.
Design: This was a prospective cross-sectional study in patients with CF (16 years and older) with clinical stability, attending the Adult CF Program at the Hospital de Clínicas de Porto Alegre. The patients had Doppler echocardiography and performed a 6MWT. As well as pulmonary function tests and chest roentgenograms, and a clinical score was obtained for all patients.
Results: The study included 39 patients with a mean age of 23.7±6.3 years. There were no significant correlation between the distance walked and PASP, diameter of the right ventricle (DRV) and pulmonary acceleration time ($p>0.05$). We observed a significant correlation among PASP and the SpO_2 at rest ($r=-0.73$; $p<0.001$), SpO_2 at the end of the 6MWT ($r=-0.45$; $p=0.006$), clinical score ($r=-0.55$; $p=0.001$), chest radiograph score ($r=-0.33$; $p=0.049$), FEV1 ($r=-0.63$; $p<0.001$), and FVC ($r=-0.55$; $p=0.001$). Right ventricular outflow tract flow acceleration time (Ac T) was significantly correlated only with the FEV1 ($r=0.32$; $p=0.047$). RVD was significantly correlated with SpO_2 at rest ($r=-0.44$; $p=0.005$) and clinical score ($r=-0.38$; $p=0.017$). The SpO_2 at rest was the single best predictor of PASP and this effect was independent of the relationship between other independent variables ($p=0.001$). The declining pulmonary function was significantly associated with PASP ($p<0.001$), SpO_2 at rest ($p=0.001$), SpO_2 at the end of the 6MWT ($p=0.007$) and difference between peripheral oxygen saturation at resting and at the end of the 6MWT ($p=0.025$).
Conclusion: The PASP was not significantly correlated with the distance walked during the 6MWT in patients with CF. The PASP was strongly correlated with oxygen status at rest. The SpO_2 at rest was the best predictor of PASP. Also, PASP was strongly correlated with Shwachman–Kulczycki score, FEV_1, and FVC in this population.

Keywords: Cystic fibrosis; Pulmonary arterial systolic pressure; Exercise; Doppler echocardiography; Six-minute walk test

1. Introduction

In patients with cystic fibrosis (CF), continuous pulmonary infection and inflammation with thickened secretions cause airways obstruction and hyperinflation. [1] As the disease progresses, these patients develop disabling lung

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* Corresponding author. St. Domingos Crescêncio 185/502, CEP: 90650-090, Porto Alegre, RS, Brazil.
E-mail addresses: larove_@hotmail.com, provedder@ig.com.br (P.M.E. Rovedder).

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disease and eventually respiratory failure and pulmonary hypertension (PH) [2].

PH is considered to be a consequence of several mechanisms that either raise the pressure downstream of the pulmonary capillaries, induce vasoconstriction, increase blood flow to the lung, or obstruct the pulmonary vessels either by embolism or in situ fibrosis. The pathophysiology of PH and cor pulmonale in CF is thought to be related to progressive destruction of the lung parenchyma and pulmonary vasculature, and to pulmonary vasoconstriction secondary to hypoxemia [3,4].

The echocardiogram is an integral part of the evaluation of a patient with PH. Common echocardiographic findings in PH includes right atrial and right ventricular (RV) enlargement, reduced RV function, displacement of the intraventricular septum to the left, and tricuspid regurgitation that permits the estimation of the pulmonary artery systolic pressure (PASP) [5–7]. In CF, as in other lung diseases, desaturation is accentuated during exercise [8]. Episodic hypoxemia and hypercapnia may occur during times of physiologic stress in CF, namely exercise. It has been proposed that during exercise moderate hypoxemia and hypercapnia occur because of wasted ventilation and expiratory flow limitation. It has also been proposed that exercise limitation in CF is greatest in those with diminished nutritional status [9].

The ability to walk for a distance is a quick and inexpensive measure of physical function, and an important component of quality of life since it reflects the capacity to undertake day-to-day activities [10].

The six-minute walk test is a submaximal exercise test that can be performed by a patient intolerant of maximal exercise tests. The test is very simple, requires inexpensive equipment, and is reproducible. In addition, it is considered safe because patients are self-limited during exercise. Recently the distance walked in 6 min has been shown to correlate significantly with maximal oxygen uptake [11].

The objectives of this study were (1) to assess the relation between PASP and the distance walked during the six-minute walk test (6MWT) in patients with CF, (2) to determine the relation between PASP and exercise induced hypoxemia by using the 6MWT, and (3) to investigate the relation between echocardiographic findings and results of 6MWT clinical scores (Shwachman–Kulczycki) [12], chest radiograph scores (Brasfield) [13] and lung function tests.

2. Materials and methods

2.1. Patient population

CF patients (≥16 years old) confirmed by an abnormal sweat test result were recruited from the Adult CF Program at Hospital de Clínicas de Porto Alegre (HCPA). We recruited 14 patients with severe lung disease (FEV_1 <40% of the predicted normal value), 12 patients with moderately severe lung disease (FEV_1 40 to 65% predicted), and 13 patients with mild lung disease (FEV_1 >65% predicted). All patients were in clinically stable condition. Patients were excluded if they had a known primary cardiac disease (such as congenital heart disease, rheumatic valve disease, or pericarditis), if they had received domiciliary oxygen therapy, or if they were pregnant.

2.2. Study design

This was a single-center, prospective cross-sectional study in which all patients attending the Adult CF Program at HCPA who volunteered for the study were included. Each CF patient had a comprehensive evaluation of their health status with the assessment of clinical stability by a senior member of the research team. In the same week a Doppler echocardiographic study, a pulmonary function test, a chest-x ray, and a 6MWT were performed with all patients. The protocol was approved by the HCPA Ethics Committee and informed consent was obtained from each patient.

2.3. Six-minute walk test

The distance the patient was able to walk in 6 min was determined using a corridor of 30 m long, following a standardized protocol [14]. The patients were instructed to walk as far as possible for 6 min under the supervision of a physiotherapist. Technicians encouraged subjects with the standardized statements, “You are doing well” or “Keep up the good work,” but were asked not to use other phrases [14]. The total distance walked and the initial and final SpO_2 were recorded by pulse oximetry (NPB-40; Nellcor Puritan Bennett; Pleasanton; USA). Two tests were done and the best result was reported. All patients tolerated the six-minute walk test without any adverse effects.

2.4. Echo-Doppler studies

M-mode, two-dimensional, and Doppler echocardiography (ATL-HDI 5000; Washington; USA) were performed from the standard parasternal, apical, and subcostal views in the resting state, in the semisupine, left lateral position, by the same observer blinded to the clinical status of the patients.

PASP was measured from the continuous-wave Doppler signal of the tricuspid regurgitation gradient by the simplified Bernoulli equation ($Dp = 4v^2$, where Dp is the peak pressure difference between right ventricular and right atrium, and v is the peak flow velocity of the tricuspid regurgitant jet) and added to the right atrial pressure, which was assumed to be 10 mm Hg. PASP was considered elevated when greater than 35 mm Hg [15]. From the pulmonary forward flow trace, the pulmonary acceleration time (Ac T) was calculated as the time interval between the onset of flow and the peak flow velocity. The right ventricular dimension was measured at end diastole from M-mode traces and by using the recommendations of the American Society of Echocardiography [16].

Table 1
Characteristics of patients according values of the PASP

Variable	PASP<35 mm Hg (n=16)	PASP≥35 mm Hg (n=23)	RR	CI 95%	p value
Age (years)	21.4±4.7	25.2±6.8	1.01	1.00–1.02	0.065
Age at diagnosis (years)	11.0±9.4	11.6±11.8	1.00	0.99–1.00	0.865
Sex (male/female)	5/11	13/10	1.52	0.89–2.58	0.258
BMI (kg/m^2)	20.3±2.4	20.7±2.5	1.00	0.97–1.04	0.641
S–K clincal score	84.3±10.3	71.5±11.0	0.98	0.98–0.99	0.001
Brasfield score	18.3±3.2	14.8±3.9	0.96	0.94–0.98	0.007
FEV_1 (% predicted)	71.9±28.5	44.3±19.8	0.99	0.98–0.99	0.001
FVC (% predicted)	78.8±21.3	60.3±19.8	0.99	0.98–0.99	0.009
Physical activity (% of yes)	41%	59%	1.19	0.61–1.75	0.894
6MWT					
Distance (m)	560.1±88.7	559.7±69.9	0.99	0.99–1.00	0.988
SpO_2 at rest (%)	98.0±0.8	95.8±1.8	0.91	0.87–0.94	<0.001
SpO_2 at the end (%)	96.7±2.0	92.4±6.6	0.98	0.96–0.99	0.017
ΔSpO_2 (%)	1.3±2.2	3.7±5.3	1.01	1.00–1.02	0.101
HR at rest (bpm)	84.8±11.68	86.0±12.6	1.00	0.99–1.00	0.771
HR at end (bpm)	123.6±21.4	123.7±21.5	0.99	0.99–1.00	0.900

Data are presented as the mean±SD.
PASP=pulmonary artery systolic pressure; BMI=body mass index; S–K=Schwachman–Kulczycki; FEV_1=forced expiratory volume in the first second; FVC=forced vital capacity; 6MWT=six-minute walk test; SpO_2=peripheral oxygen saturation; ΔSpO_2=difference between peripheral oxygen saturation at resting and in the end 6MWT; HR=heart rate.
Student's t test for continuos variables and chi-square test for categorical variables.

2.5. Clinical and radiographic scores

The clinical score was performed by the same senior member of the CF team in the out-patient setting, using the Shwachman–Kulczycki scoring system [12].

All chest roentgenograms of CF patients were scored using the Brasfield scoring system [13] by the same senior member of the research team. This observer was blinded to the clinical severity status of the patients.

2.6. Pulmonary function tests

Spirometry was measured with computerized spirometer (Jaeger — v 4.31; Wuerzburg; Germany). FVC, FEV_1 and FEV_1/FVC were measured three times, and the best result was reported. All parameters were expressed as percent predicted for age, stature, and gender [17].

2.7. Statistical analysis

Data are expressed as proportion or mean±standard deviation (SD). Student's t test was used for comparison between groups with PASP <35 mm Hg and with PASP ≥35 mm Hg. Categorical comparisons were performed by chi-square test. Relative risk was calculated for the characteristics of patients classified according values of the PASP greater or equal to 35 mm Hg. Correlations were determined using Pearson linear correlation. Stepwise forward linear (method enter) was performed for independent variables associated significantly with PASP. Sensitivity, specificity and predictive values were calculated for different cutoffs of a SpO_2 at rest to predict PASP of 35 mm Hg or greater. Data from the three groups of lung function were evaluated with a one-way analysis of variance and a pos-hoc test multiple comparisons (Tukey test) was performed. Data analysis was carried out using the SPSS software package, version 13.0 and Stata statistical software (Stata, College Station, TX). The statistical significance level was set at $p<0.05$. All probabilities reported were two-tailed. We calculated the sample size, using a correlation coefficient of $r=0.5$ between the PASP and the distance walked in 6MWT noted in the first 5 CF patients. An

Table 2
Correlation between echocardiographic findings and results of 6MWT, clinical scores (Shwachman–Kulczycki), chest radiographs scores (Brasfield) and lung function tests

Variable	PASP	Ac T	RVD
Walk distance	r=−0.25	r=0.10	r=0.15
	p=0.141	p=0.564	p=0.362
SpO_2 at rest	r=−0.73	r=0.06	r=−0.44
	p<0.001	p=0.702	p=0.005
SpO_2 at end 6MWT	r=−0.45	r=0.26	r=−0.24
	p=0.006	p=0.112	p=0.136
S–K clinical score	r=−0.54	r=0.30	r=−0.38
	p=0.001	p=0.067	p=0.017
Brasfield score	r=−0.33	r=0.27	r=−0.31
	p=0.049	p=0.107	p=0.054
FEV_1 (% predicted)	r=−0.63	r=0.32	r=−0.31
	p<0.001	p=0.047	p=0.053
FVC (% predicted)	r=−0.55	r=0.30	r=−0.21
	p=0.001	p=0.064	p=0.190

PASP=pulmonary artery systolic pressure; Ac T=Right ventricular outflow tract flow acceleration time; RVD=right ventricle dimension; 6MWT=six-minute walk test; S–K=Schwachman–Kulczycki; SpO_2=peripheral oxygen saturation; FEV_1=forced expiratory volume in the first second; FVC=forced vital capacity; r=Pearson correlation coefficient. Pearson linear correlation.

adequate sample size in the present study was found to be at least 38 subjects $\propto = 0.05$ and $1-\beta = 90\%$.

3. Results

Thirty-nine of 41 patients attending the Adult CF Program at HCPA were included in the study. One patient refused to participate in the study. Another patient was excluded from the study because she was receiving domiciliary oxygen therapy. The mean age of our patients was 23.7±6.3 years (range from 16 to 47). There were 21 female and 18 male patients. All patients were Caucasian. The mean body mass index was 20.5±2.5 kg/m^2 (range form 16.5 to 28.1). During the 6MWT test, subjects walked a mean distance of 559.9±77.1 m (range from 420 to 714).

The right ventricular outflow tract flow acceleration time Ac T could not be obtained in one patient because hyperinflation of the chest limited visualization of the Doppler signal of tricuspid regurgitation. In three patients the tricuspid regurgitation gradient could not be determined and consequently the PASP could not be determined. These patients were analyzed in the group with normal PASP.

Table 1 summarizes the characteristics of patients according values of the PASP found in our patients. PASP was greater than 35 mm Hg in 23 patients. This group presented decreased values of clinical score, chest radiograph score, FEV_1 % predicted, FCV % predicted, and peripheral oxygen saturation at rest and at the end of the 6MWT significantly compared to normal PASP ($p<0.05$).

Pearson linear correlation analysis (Table 2) showed that PASP was not significantly correlated with the distance walked in 6 min ($r=-0.25$; $p=0.141$, Fig. 1). The PASP was significantly correlated with SpO_2 at rest ($r=-0.73$; $p<0.001$, Fig. 2), SpO_2 at the end of the 6MWT ($r=-0.45$; $p=0.006$), clinical score ($r=-0.55$; $p=0.001$), chest radiograph score ($r=-0.33$; $p=0.049$), FEV_1 ($r=-0.63$; $p<0.001$), FVC ($r=-0.55$; $p=0.001$). The Ac T was

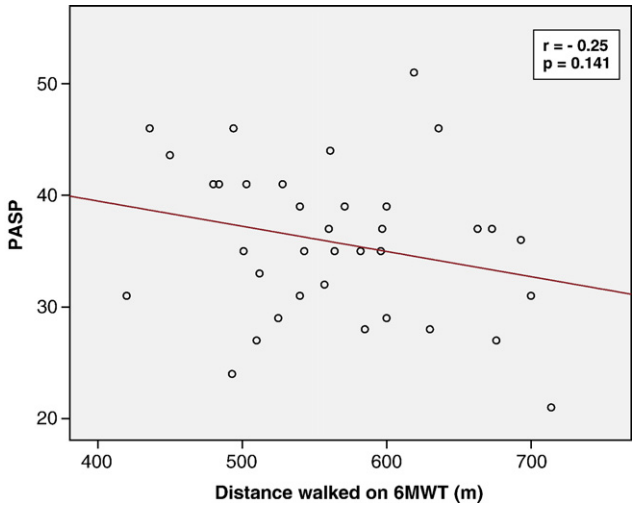

Fig. 1. Correlation between PASP and the distance walked on 6MWT.

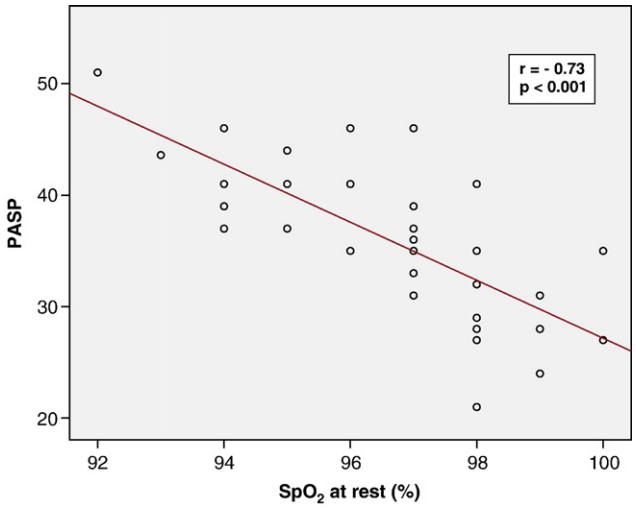

Fig. 2. Correlation between PASP and peripheral oxygen saturation at rest.

significantly correlated only with the FEV_1 ($r=0.32$; $p=0.047$). RVD was significantly correlated with SpO_2 at rest ($r=-0.44$; $p=0.005$) and clinical score ($r=-0.38$; $p=0.017$). In the stepwise forward linear (method enter) we observed (Table 3) that SpO_2 at rest was the single best variable associated with PASP and that this effect was independent of the relationship between other independent variables ($p=0.001$).

We calculated sensitivity, specificity and predictive values for different cutoffs of a SpO_2 at rest to predict PASP of 35 mm Hg or greater. For a cutoff of 96% or less in SpO_2 at rest we found a sensitivity of 56%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 62,9%.

Pearson linear correlation analysis showed that BMI was not significantly correlated with the distance walked in 6MWT ($r=0.17$; $p=0.290$), PASP ($r=0.01$; $p=0.938$), Ac T (-0.06; $p=0.735$) and RVD ($r=0.14$; $p=0.404$).

Characteristics of patients according lung function are summarized in Table 4. Declining pulmonary function was significantly associated with PASP ($p<0.001$), SpO_2 at rest ($p=0.001$), SpO_2 at the end of the 6MWT ($p=0.007$) and

Table 3
Linear regression analysis for variables associated with PASP

Variable	*B*	Beta	95% CI	*p* value
Sex	1.57	0.12	−2.10–5.25	0.387
Age (years)	−0.04	−0.04	−0.35–0.27	0.787
S–K clinical score	−0.11	−0.20	−0.34–0.13	0.354
Brasfield score	0.22	−0.13	−0.34–0.77	0.429
FEV_1 (% predicted)	−0.05	−0.18	−0.18–0.08	0.462
SpO_2 at rest (%)	−2.62	−0.74	−4.08–−1.17	0.001
SpO_2 at end 6MWT(%)	0.19	0.16	−0.21–0.59	0.334

PASP=pulmonary artery systolic pressure; S–K=Schwachman–Kulczycki; FEV_1=forced expiratory volume in the first second; SpO_2=peripheral oxygen saturation; 6MWT=six-minute walk test; *B*=coefficient angular. Linear regression analysis (method enter).

Table 4
Characteristics of patients according with lung function

Patients characteristics	Mild lung disease ($n=13$)	Moderate lung disease ($n=12$)	Severe lung disease ($n=14$)	p value
Age (years)	20.5±4.9	25.0±5.5	25.5±7.3	0.075
Sex (male/female)	4/9	7/5	7/7	0.354
PASP	29.3 ± 4.5^{A}	38.0 ± 3.7^{B}	39.8 ± 6.5^{B}	<0.001
FEV_1 (% predicted)	89.1 ± 15.1^{A}	48.8 ± 8.0^{B}	30.5 ± 7.1^{C}	<0.001
FVC (% predicted)	93.3 ± 11.8^{A}	64.5 ± 11.0^{B}	47.22 ± 9.2^{C}	<0.001
Distance 6MWT(m)	589.1±92.3	564.3±53.1	529.0±72.1	0.124
SpO_2 at rest (%)	98.1 ± 1.1^{A}	96.3 ± 1.1^{B}	95.8 ± 2.1^{B}	0.001
SpO_2 at the end 6MWT(%)	97.3 ± 2.0^{A}	94.8 ± 3.0^{AB}	90.8 ± 7.7^{B}	0.007
ΔSpO_2 (%)	0.92 ± 2.2^{A}	1.7 ± 1.8^{AB}	5.2 ± 6.4^{B}	0.025

Data are presented as the mean±SD.
PASP=pulmonary artery systolic pressure; FEV_1=forced expiratory volume in the first second; FVC=forced vital capacity; 6MWT=six-minute walk test; SpO_2=peripheral oxygen saturation; ΔSpO_2=difference between peripheral oxygen saturation at resting and in the end 6MWT.
Analysis-of-variance for continuous variables and chi-square test for categorical variables and pos-hoc test (Tukey test): means significantly different if different letters; AB does not differ from A or B.

difference between peripheral oxygen saturation at resting and at the end of the 6MWT ($p=0.025$).

4. Discussion

In this study, we found no significant correlation between the PASP and the distance walked during the 6MWT in patients with CF. Twenty-three of 39 (59%) patients presented PASP≥35 mm Hg. The mean distance walked during the 6MWT in patients with PASP≥35 mm Hg was 559.7±69.9 m, and in patients with PASP<35 mm Hg it was 560.1±88.7 m. Our findings are consistent with a previous report by Miyamoto et al. [11], who demonstrated in patients with primary pulmonary hypertension (PPH) that the distance walked in 6MWT was not significantly correlated with mean pulmonary arterial pressure. In our study, one possible reason for this finding was that every patient studied was young, with a mean age of 23.7 years, in stable condition, and carrying on with normal daily living activities.

Although no correlation with PASP was demonstrated, the distance walked in 6MWT can provide an assessment of a different clinical dimension in patients with respiratory disability. The 6MWT is a simple and non-expensive test that can provide a global evaluation of exercise capacity and the distance walked is the most important outcome measure [18]. The 6MWT has been used as a parameter of physical function and to correlate the capacity to undertake daily activities [10,19,20]. Several authors [2,11,20–23] have shown that the 6MWT is of great prognostic value in PH.

Although the three groups of lung function severity had a similar performance in terms of distance walked, the groups showed a significant increase of the PASP, according to declining pulmonary function, and a significant increase in the degree of desaturation during the 6MWT (Table 4). Our findings are consistent with a previous report by Chetta et al. [24] who demonstrated that the walk distance covered by young adults with CF and ventilatory impairment was the same as that covered by an age- and sex-matched control group. It is therefore unlikely that peripheral oxygen delivery was limiting in these patients. Maximum exercise capacity in patients with CF depends on the severity of the impairment in lung function and on the severity of the oxygen desaturation [25,26]. However, 6MWT can be considered as an endurance, submaximal exercise test, since it demands the ability to sustain the exercise, rather than the capacity for maximum exercise. Generally more vigorous exercise causes greater desaturation than the exercise in 6MWT.

Both intermittent and sustained hypoxemia have been implicated in the pathogenesis of PH in animal models [27,28] and in human studies [2]. In our study, the PASP was significantly correlated with SpO_2 at rest and SpO_2 during 6MWT. Furthermore, the regression analysis showed that SpO_2 at rest was predictive of elevated PASP, independent of other variables. One of the most surprising findings in our study was the large number of subjects with resting saturations greater than or equal to 95% with elevated PASP. It seems difficult to explain the raised PASP on the basis of exercise desaturation. Chronic hypoxia is hard to accept given that the lowest resting saturation was 92% and only 2 patients were below 94%. Support for this finding comes from studies in CF and stable lung disease [2,5]. It was demonstrated that subclinical PH develops in a substantial proportion of patients with CF and stable lung disease and that it correlates with the frequency and severity of episodes of arterial oxygen desaturation and with FEV_1. A potential relationship linking inflammation at the end of respiratory exacerbation and PH was suggested [5]. Moreover, some CF patients may have excessive oxygen desaturation during sleep, which may exert a cumulative effect leading to PH [2].

PASP was significantly correlated with declining pulmonary function (FEV_1 and FVC) (Table 2). Pulmonary arterial hypertension (PASP≥35 mm Hg) was found in 10 of 14 subjects (71%) with severe lung disease, in 10 of 12 subjects (83%) with moderate lung disease and in 3 of 13 subjects (23%) with mild lung disease without clinical signs of cor

pulmonale. Fraser et al. [2] estimated that up to 40% of the population of adult patients (>18 years old) with CF and severe lung disease have PH without clinical signs of cor pulmonale. Patients with better pulmonary function (FEV1>40% predicted) found a higher incidence of pulmonary hypertension.

In this study, we saw a significant difference in clinical score of patients with PASP ≥35 mm Hg and patients with normal PASP ($p=0.001$). The clinical score was also moderately correlated with the values of PASP and RVD. Moderate correlation between the chest radiograph scores and the PASP was also demonstrated.

In our study the mean age of diagnosis was 11.4 years old, which surely must be late. This may have resulted in more pulmonary vascular changes than would be suggested from spirometric values. However, several limitations of using age of diagnosis as a discriminate variable should be acknowledged. In addition to differences in phenotype, delay in diagnosis may be influenced by a variety of nonclinical factors, such as access to and quality of health care, and implementation of newborn screening [29]. Although newborn screening is too recent a development to have affected our study population, in the future, newborn screening may decrease the proportion of individuals diagnosed at later ages. Moreover, it was widely assumed that much of the variability in disease phenotype would be explained by difference in gene mutations [30]. Additional study analyzing pulmonary hypertension and genotype would clarify this question.

4.1. Implications of findings

The PASP was demonstrated to have association with several variables such as SpO_2 at rest, SpO_2 at the end of the 6MWT, clinical score, chest radiograph scores, FEV_1, and FVC. Among these variables, however, only SpO_2 at rest was the best predictor of PASP. But there are many patients with a normal resting saturation and an elevated PASP. It may thus be useful to monitor PASP in CF patients with chronic lung disease, despite normal resting oxygen saturation. Otherwise, the 6MWT could contribute to unmasking more advanced pulmonary vascular disease.

4.2. Limitations of study

The present study has several limitations. Studies in patients with cardiac disease have revealed a significant statistical correlation between PASP estimated by Doppler echocardiography and that measured by right heart catheterization [5,31,32]. However, in patients with chronic pulmonary disease, Doppler echocardiography has been reported to perform variably in the assessment of PASP. Despite a close correlation between Doppler echocardiography estimated and directly measured PASP, several studies have revealed that such estimations were possible in only a minority of patients with chronic pulmonary disease. If Doppler echocardiography were to consistently overestimate or underestimate PASP by a constant value, correlation would be high, but the accuracy of the estimation would be dictated by the magnitude of the discrepancy. Despite a statistically significant correlation with directly measured values, estimation of PASP by echocardiography is frequently inaccurate in patients with advanced lung disease and leads to considerable overdiagnosis of PH [32,33].

The technique employed to estimate PASP by echocardiography involves calculation of the trans-tricuspid gradient from measuring the peak velocity of the tricuspid regurgitation jet using the modified Bernoulli equation [16]. Right ventricular pressure and, indirectly, PASP are then determined by adding an estimated right atrial pressure to calculated trans-tricuspid gradient [16]. The success and accuracy of this technique are dependent on the ability to identify and precisely measure the velocity of the tricuspid regurgitant jet and, therefore, are influenced by factors altering the position of the heart in relationship to the Doppler echocardiography probe such as obesity, thorax deformities, and lung hyperinflation [34]. In our study, the tricuspid regurgitation gradient could not be determined in three patients and in consequence the PASP could not be estimated. These patients were analyzed in the group with normal PASP. It was not possible to measure the right ventricular outflow tract flow acceleration time in one patient. Furthermore, the intraobserver and interobserver variability and limitations in the estimation of PASP can also impact upon the accuracy of this technique [34]. In the current study, one experienced cardiologist performed all the analyses, so that it is difficult to assess whether there was any bias in the estimates, and, if so, in which direction.

In conclusion, we demonstrated that the PASP was not significantly correlated with the distance walked during the 6MWT in patients with CF. The PASP was strongly correlated with oxygen status at rest. The SpO_2 at rest was the best predictor of PASP. Also, PASP was strongly correlated with Shwachman–Kulczycki score, FEV_1, and FVC in this population.

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