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Functional capacity assessment during exercise in children and adolescents with post-infectious bronchiolitis obliterans

**Rita Mattiello,[1] Edgar E. Sarria,[2] Ricardo Stein,[3] Gilberto Bueno Fischer,[4]
Helena Teresinha Mocelin,[5] Sergio Saldanha Menna Barreto,[4]
João Antônio Bonfadini Lima,[6] Diego Brandenburg[7]**

Abstract

Objective: To assess functional capacity during exercise in children and adolescents with post-infectious bronchiolitis obliterans (PIBO).

Methods: 20 children with PIBO, aged 8-16 years old, and in follow-up at an outpatient clinic carried out cardiopulmonary exercise testing (CPET), a 6-minute walk test (6MWT) and pulmonary function tests (PFT), according to American Thoracic Society (ATS), European Respiratory Society (ERS) and American College of Chest Physicians (ACCP) guidelines. Results were expressed as percentages of predicted reference values: Armstrong's for CPET, Geiger's for 6MWT, Knudson's for spirometry, and Zapletal's for plethysmography.

Results: Mean age (± SD) was 11.4±2.2 years; 70% were boys; mean weight: 36.8±12.3 kg; mean height: 143.8±15.2 cm. When compared to reference values, PFT detected lower airflows (spirometry) and higher volumes (plethysmography). Eleven patients had reduced peak VO_2 values in CPET (< 84% predicted). The mean distance walked (6MWT) was 77.0±15.7% of predicted (512±102 m). Peak VO_2 was not correlated with 6MWT, but it was correlated with FVC (L) ($r = 0.90/p = 0.00$), with FEV_1 (L) ($r = 0.86/p = 0.00$) and with RV/TLC, both in absolute values ($r = -0.71/p = 0.02$) and as percentages of predicted values ($r = -0.63/p = 0.00$).

Conclusions: The majority of these post-infectious bronchiolitis obliterans patients exhibited reduced functional capacity, exhibited during both CPET and the 6MWT. Due to its greater feasibility, 6MWT could be an alternative where CPET is not available.

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Introduction

Post-infectious bronchiolitis obliterans (PIBO) is a chronic lung disease that results from some type of aggression to the lower respiratory tract in previously healthy children. From the pathological perspective, PIBO is characterized by obstruction of the lumen with granulation tissue, inflammation and fibrosis with obliteration of small airways and bronchiectasis.[1]

Functional assessment of PIBO patients at rest demonstrate airflow limitation, characterizing an obstructive ventilatory disorder that is generally severe and irreversible.[2] This

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1. MSc. Doctoral Student in Pediatrics, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil.
2. PhD. Research assistant, Universidad de Santiago de Chile, Chile.
3. PhD. Professor, Cardiology Postgraduate Course, UFRGS, Porto Alegre, RS, Brazil.
4. PhD. Professor, Pediatrics Postgraduate Course, UFRGS, Porto Alegre, RS, Brazil.
5. PhD. Pediatric Pulmonology Section, Hospital da Criança Santo Antônio, Porto Alegre, RS, Brazil.
6. MSc. Doctoral Student in Pulmonology, UFRGS, Porto Alegre, RS, Brazil.
7. MD. Pediatric Pulmonology Section, Hospital da Criança Santo Antônio, Porto Alegre, RS, Brazil.

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airflow restriction can limit physical activity levels (PAL) among these individuals.

Exercise capacity testing is considered part of the multidimensional assessment of patients with chronic lung disease, since it objectively evaluates cardiac, respiratory, muscular, and metabolic systems.[3,4] In this context, cardiopulmonary exercise testing (CPET) is considered the gold standard for investigating the causes of exercise intolerance.[3,5]

There are few studies evaluating the pulmonary function of PIBO patients during exercise. Considering the importance of PAL in children and adolescents, particularly those with respiratory problems, and in view of the lack of scientific knowledge on the functional behavior of these individuals during exercise, the aim of this study is to assess their functional capacity during exercise.

Methods

Children and adolescents aged 8 to 16 years old and with previous diagnosis of PIBO were enrolled. They were in follow-up at the pediatric pulmonology outpatient clinic from one of two hospitals, Hospital Materno Infantil Presidente Vargas (HMIPV) or Hospital da Criança Santo Antônio (HCSA), both in Porto Alegre, RS, Brazil. Diagnosis was based on the following combination of clinical, radiological and functional criteria:[1,2] 1) history of acute pulmonary infection in a previously healthy child less than 2 years old; 2) permanent respiratory signs and symptoms (e.g. wheezing, crepitations, coughing) 4 weeks after the initial event; 3) high resolution computerized tomography with abnormalities characteristic of bronchiolitis obliterans (BO), such as mosaic pattern, bronchiectasis and atelectasis; 3) airflow limitation demonstrated by pulmonary function tests; and 4) exclusion of other chronic lung conditions with a clinical course involving persistent respiratory symptoms, such as severe asthma, cystic fibrosis, alpha-1-antitrypsin deficiency and immunodeficiencies, among others.

Patients were excluded if they had: 1) cognitive or motor limitations, or any other condition that could compromise performance of the tests; 2) pulmonary or systemic hypertension and electrocardiographic findings suggestive of heart disease (rhythm/conduction disorders and/or ST segment abnormalities); 3) deterioration of their respiratory status during the 30 days prior to the tests, denoted by worsening of signs and symptoms (coughing, wheezing, expectoration, dyspnea) or infection.

Patients were instructed not to drink coffee, tea or soft drinks, nor to eat chocolate or to perform exercise during the 2 hours prior to the tests and also not to use bronchodilators prior to testing, 8 hours for short acting and 24 hours for long acting.

This study was approved by the Research Ethics Committees at the HMIPV and the Hospital de Clínicas de Porto Alegre. The children indicated their willingness to participate verbally and their guardians signed free and informed consent forms.

Three appointments were made for each participant to be tested. At the first visit, patient history was taken, a physical examination carried out, nutritional status and PAL were assessed and the patient performed a 6-minute walk test (6MWT).[6] The pulmonary function tests were performed at the second visit and the patient underwent CPET at the third appointment. All interviews were conducted by the same interviewer, and all clinical assessments were carried out by a single pediatric pulmonologist. The minimum interval between appointments was 2 days, and the maximum was 14 days.

Nutritional assessment

Weight and height were measured for nutritional assessment. These were then used to calculate body mass index (kg/m^2), which was classified according to the Centers for Disease Control (CDC) reference values, by age and sex.[7] All measurements were taken by the same examiner, with instruments properly calibrated and employing standardized measurement techniques.[8]

Pulmonary function

American Thoracic Society (ATS) technical procedures as well as acceptability and reproducibility criteria were used for pulmonary function tests.[9,10] Spirometry and plethysmography were carried out using a Master-Screen equipment (Jaeger, Germany), and the following parameters were recorded: 1) spirometry: forced vital capacity (FVC), forced expiratory volume in 1 second (FEV$_1$), FEV$_1$ to FVC ratio (FEV$_1$/FVC), forced expiratory flow between 25-75% of FVC (FEF$_{25-75\%}$); and 2) plethysmography: total lung capacity (TLC), intrathoracic gas volume (ITGV), residual volume (RV), RV to TLC ratio (RV/TLC). These data are given as percentage of predicted values according to Knudson[11] for spirometry, and Zapletal[12] for plethysmography.

Physical Activity Questionnaire

The full version of the International Physical Activity Questionnaire (IPAQ) was applied by interview. The time spent performing the different IPAQ domains was calculated from the product of the duration (minutes/day) and the frequency (days/week) patients reported for each activity type and then, from these results, they were categorized as having low, moderate or intense PAL.[6]

Submaximal exercise test

The 6MWT was conducted in accordance with ATS recommendations.[13] In common with pulmonary function tests, patients remained at rest for 30 minutes before starting the 6MWT. The following parameters were assessed before and after the test: pulmonary auscultation (PA), heart rate (HR), respiratory rate (RR), peripheral oxygen saturation (SaO$_2$)

(Nonin's WristOx® 3100, USA), peak expiratory flow (PEF) and the Borg scale (perceived exertion scale for lower limbs and dyspnea). Peak expiratory flow was assessed at 3, 5, 10, 15 and 20 minutes after the test. A fall in PEF was considered significant if there was a variation of ≥ 15% between post and pre measurement [((PEF post - PEF pre)/PFE post) x 100]. Total distance walked was also recorded. Each child was asked to walk as far as possible in 6 minutes, along a 30 m corridor. Once a minute they were encouraged verbally, using phrases recommended by the ATS. The following were criteria for halting the test: intense tiredness and dyspnea as expressed by the patient; $SaO_2 \leq 80\%$ or refusal to continue the test. The reference values published by Geiger et al. were used to calculate the percentage of predicted distance that was actually walked.[14]

In order to assess maximum heart rate during the 6MWT and CPET, an estimated heart rate formula was employed, based on patient's age [205 - (0.5 x age in years)].[15]

Maximal exercise test

Cardiopulmonary exercise testing was conducted by a cardiologist proficient in the method, with the aid of a pediatric pulmonologist and a physiotherapist. Tests were carried out in accordance with ATS and the American College of Chest Physicians recommendations.[5] All tests were performed during the morning, at room temperature of 22 to 24 ºC and relative humidity of aproximately 60%.

Maximal cardiopulmonary testing was carried out using a computerized system (Metalyzer 3B, Cortex, Germany) and a treadmill (Inbramed® KT 10200, Brazil) with velocity in the range of 0 to 16 km/h (0 to 10 mph) and a ramp angle ranging from 0 to 26%.

At the start of the test, the subject walked for around two minutes to become accustomed to the treadmill. The protocol began at a velocity of 2.4 km/h with a 2% incline. Velocity was increased every 20 s (0.1 to 0.2 km/h), and inclination was increased every 60 s (0.1 to 0.2%). During the test patients were encouraged by the same person to maintain their rhythm until exhaustion or until limiting symptoms appeared. The exercise intensity was calculated with the intention that the test lasted approximately 8 to 10 minutes.

The following variables were analyzed (breath by breath) using a previously validated system:[16] oxygen consumption (VO_2), in mL/min, STPD (Standard Temperature and Pressure, Dry); carbon dioxide output (VCO_2), in mL/min, STPD; respiratory exchange coefficient (R); minute volume (VE), in L/min, BTPS (Body Temperature, Pressure Saturated); respiratory rate (RR) and heart rate (HR). Peak VO_2 was defined as the highest value observed during the last 20 s of exercise and we used reference values published by Armstrong et al..[17]

Cardiopulmonary parameters were recorded before and after the test pulmonary and cardiac auscultation, SaO_2, RR, HR, blood pressure, PEF and Borg). Oxygen saturation and electrocardiographic tracing were continuously monitored, using, respectively, a pulse oximeter (Nonin's WristOx® 3100, United States) and a cardiac monitor (Nikon Kohden Corporation®, Japan). Peak expiratory flow was measured at 3, 5, 10, 15 and 20 minutes after the test. Blood pressure (BP) was measured using an aneroid sphygmomanometer (Tycos®, United States).

Statistical analysis

Data were analyzed using SPSS version 14.0 (SPSS Inc, United States). The distribution of variables was analyzed using the Kolmogorov-Smirnov test. Continuous variables are presented in the form of means and standard deviations or medians and interquartile ranges; categorical measures are given as absolute and relative frequencies. The results of pulmonary function and exercise tests are given as percentages of predicted values. Student's *t* test was used for comparisons between means of variables with normal distribution, while the Wilcoxon test was used for measures that exhibited asymmetrical distribution. Correlations between pulmonary function and exercise test variables were assessed using Pearson's correlation coefficient (r). Based on a sample of 20 patients, accepting an alpha error of 5% and a beta error of 20%, correlations were accepted at $r \geq 0.6$.

Results

A total of 73 children with PIBO were in follow-up at the two institutions. Of these, 20 met the inclusion criteria and took part in the study. Their mean age was 11 years, and 70% were male. In terms of nutritional status, the majority were well-nourished (16 patients), three were classified as malnourished and one as overweight.

The IPAQ results classified 17 patients (85%) as active (four with intense PAL), three (15%) were classified as not very active and none of the patients were classified as sedentary. No correlations were observed between PAL and peak oxygen consumption ($r = 0.14/p = 0.57$).

When compared to the reference population, these patients exhibited reduced forced flows on spirometry, and increased volumes on plethysmography (Table 1).[11,12]

Three patients did not perform the CPET because they did not attend their appointments. Three of the 17 who did undergo CPET exhibited dyspnea and an important fall in saturation at the end of the test. None of the subjects exhibited abnormalities on electrocardiogram before, during or after exercising, and the respiratory quotient (R) reached a mean of 1.0±0.6. Mean peak VO_2 (absolute value) was reduced in comparison with reference values (1.2±0.5 vs. 1.7±0.6; $p = 0.00$). This reduction is more evident when mean percentage of the predicted value is compared with the cutoff point of normality (≥ 84%)[17] (Table 1).

All of the individuals completed the 6MWT. The mean distance covered was shorter than for the reference population

Table 1 - Characteristics of pulmonary function at rest in patients with post-infectious bronchiolitis obliterans

	Mean ± SD	**(%)***
Spirometry		
FVC (L)	1.7±0.6	66.8±17.3
FEV_1 (L)	0.9±0.4	57.7±17.9
FEV_1/FVC (%)	57.9±12.5	
$FEF_{25-75\%}$ (L)	0.5±0.2	20.4±12.6
Plethysmography		
TLC (L)	4.1±1.1	121.2±23.2
ITGV (L)	3.0±0.7	186.8±46.4
RV (L)	2.4±0.7	294.3±83.3
RV/TLC (%)	59.1±8.4	
6MWT		
Distance (m)	512±102	77±15.7
CPET		
VO_2 ($L/minute^{-1}$)	1.2±0.57	77.5±37.5

6MWT = 6-minute walk test; CPET = cardiopulmonary exercise testing; $FEF_{25-75\%}$ = forced expiratory flow between 25-75% of FVC; FEV_1 = forced expiratory volume in 1 second; IFVC = forced vital capacity; RV = residual volume; SD = standard deviation; TGV = intrathoracic gas volume; TLC = total lung capacity; VO_2 = peak oxygen consumption.
* Percentage of predicted.

(512±102 vs. 665±33.5 m; p = 0.000), which, in terms of percentage of predicted, was lower than the value considered normal (≥ 80%).[14] Distance was not correlated with peak oxygen consumption, either when evaluated as absolute figures, (r = -0.28/p = 0.29) or as percentages of the predicted distance (r = -0.50/p = 0.85).

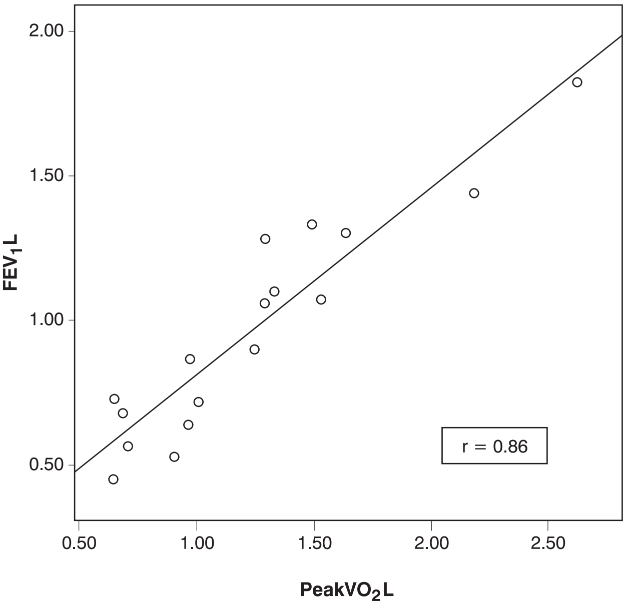
When we analyzed HR, RR and the Borg scale after the exercise test, we observed that these parameters were significantly higher in the CPET than in the 6MWT. There was a transitory drop in saturation of more than 4% in three patients in the 6MWT and in 12 patients in the CPET. A reduction in PEF (> 15%) was observed in three individuals in the 6MWT and three individuals during the CPET. On average, for the CPET versus the 6MWT, patients reached 90 *versus* 60% of maximum heart rate (Table 2).

Regarding correlations between CPET and pulmonary function tests at rest (Table 3), peak VO_2 observed during CPET correlated with absolute volumes of FVC (r = 0.90/p = 0.00), FEV_1 (r = 0.86/p = 0.00) and RV/TLC (r = -0.71/p = 0.02) (Figure 1). When peak VO_2 was treated as percentage of predicted, the only parameter with which it correlated was RV/TLC (-0.63/p = 0.00) (Table 3).

Table 2 - Comparison of variables for the 6-minute walk test and the cardiopulmonary exercise test

	6-minute walk test	**Cardiopulmonary exercise test**	
	Mean ± SD	**Mean ± SD**	**p**
Respiratory rate (PE)	30.0±3.7	57.4±9.0	0.000*
Heart rate (PE)	124.6±8.7	182.5±11.6	0.000*
Heart rate (MP)	62.5±9.4	91.6±5.8	0.000*
Minimum SaO_2	94.1±3.2	90.2±4.6	0.001*
Borg (PE)	Median (quartiles)	Median (quartiles)	
Fatigue in legs	0 (0-3)	3 (1-7)	0.005*
Dyspnea	1 (0-3)	2 (1-6)	0.047*

MP = predicted maximum heart rate; PE = post-exercise; SaO_2 min = lowest oxygen saturation during exercise; SD = standard deviation.
* $p < 0.05$



r = Pearson's correlation coefficient; FEV_1 (L) = forced expiratory volume in 1 second (Liters); VO_2 (L) = oxygem consumption

Figure 1 - Correlation between forced expiratory volume in 1 second in absolute figures and peak oxygen consumption

Discussion

The majority of patients exhibited a reduced functional capacity during exercise when submitted to CPET and 6MWT, demonstrated by their both reduced peak oxygen consumption and total distance covered when compared to reference values in healthy population.[17]

Research in pediatric patients with chronic lung conditions has reported contradictory findings on the physical performance of this population.[4,18-20] Previous studies have reported that a significant number of asthmatic children exhibit a limited capacity for exercise, characterized by reduced peak oxygen consumption.[21,22] Fanelli et al. carried out a study on 38 children with moderate to severe asthma and found that 24 patients had lower exercise capacity than healthy population.[23] However, other studies that also included patients with moderate to severe asthma have found that these patients can have a normal exercise capacity.[4,24]

Studies in children and adolescents with cystic fibrosis, a limited exercise capacity is generally associated with worse pulmonary function. Although these parameters correlate to each other, these correlations vary greatly between them, particularly between peak VO_2 and FEV_1, two indicators that showed a good correlation in our study (Figure 1). In children and adolescents, this variability can be justified by the existence of other factors related to exercise capacity, such as height, weight, puberal stage and PAL. Consequently, it is not possible to predict physical fitness solely by means of pulmonary function tests at rest.[3-5,25]

The functional characteristics of our patients, at rest, are not different from those found in other studies with PIBO, that is, characteristics of an obstructive respiratory disorder.[2,26,27] Correlations found in this study between peak VO_2 and FEV_1 and FVC with RV/TLC suggests that, in patients with PIBO, the greater the air trapping, the greater the compromise of pulmonary capacity during exercise. Nevertheless, other studies done with respiratory patients have not demonstrated the association between physical capacity and pulmonary function findings.[4,28-30]

Mocelin et al. applied the 6MWT as a submaximal test, using the same protocol we used here, to assess exercise capacity in a sample of 19 patients with PIBO.[31] The most important findings of that study were that 37% of the patients exhibited a fall in oxygen saturation during the test and that the total distance walked did not correlate with spirometric data. In our study, just 15% of the patients exhibited a reduction in SaO_2 during the 6MWT. Despite the operational advantages of the 6MWT, it does not offer the possibility of measuring the intensity needed to perform prolonged exercise, nor of quantifying its limiting factors or defining co-existing pathophysiologic mechanisms; for these purposes, CPET is the method of choice.[3,5,32]

As would be expected, when submitted to CPET, our patients exhibited significantly higher HR, RR and Borg values, and also a greater drop in saturation compared to the 6MWT. These findings are similar to what can be found in other studies using incremental testing in patients with chronic respiratory conditions. Therefore, it appears to us that maximal testing (CPET with progressive increase of the workload) can induce higher results in cardiorespiratory variables and, consequently, provide a wider range of clinically relevant data when compared with a submaximal test such as the 6MWT.[33]

Some authors recommend assessing PAL using standardized questionnaires.[34,35] However, there is conflicting evidence in the literature on the association between oxygen consumption and reported habitual PAL.[17,20] Added to this is the scarcity of this type of instruments in Brazil, particularly for younger population.[36] In this situation, researchers have to use questionnaires designed for adults, like the IPAQ. In our study, the IPAQ results patients with PIBO did not correlate with exercise test results. We believe that the absence of specific domains for activities that children take part of and the resulting under/overestimation of other activities is the main cause of these results.

The principal limitation of our study is the lack of a control group with which to compare the exercise testing results. This would also compensate for the relatively small number of patients, which limits plausible inferences that could be made based on the results, if we considering the variability of parameters included in the study. Nevertheless, since this is not a very prevalent disease, the rather homogenous group of

Table 3 - Correlations between peak oxygen consumption and pulmonary function variables at rest*

Variable	Percentage of predicted r/p	Absolute values r/p
FEV_1	0.59/0.01†	0.86/0.00†
FVC	0.59/0.01†	0.89/0.00†
FEV_1/FVC	0.37/0.13	-0.16/0.51
$FEF_{25-75\%}$	0.48/0.05	0.57/0.01†
TLC	-0.28/0.29	0.58/0.01†
TGV	-0.52/0.38	0.10/0.70
RV	-0.54/0.03†	0.12/0.64
RV/TLC	-0.63/0.00†	-0.71/0.02†

$FEF_{25-75\%}$ = forced expiratory flow between 25-75% of FVC; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; RV = residual volume; TGV = intrathoracic gas volume; TLC = total lung capacity.
* Correlations between variables in absolute values and as percentages of predicted (Knudson: spirometry, Zapletal: plethysmography, Armstrong: peak oxygen consumption).
r = Pearson's correlation coefficient.
† $p < 0.05$.

patients studied offers an important initial view of their pathophysiologic behavior when submitted to exercise. We can conclude, based on our results, that the majority of patients with PIBO studied exhibit reduced capacity for exercise, both in CPET and the 6MWT. Due to the ease of application of the 6MWT, it can be used as an alternative for the initial evaluation of patients at places that do not have access to CPET equipment.

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Correspondence:
Rita Mattiello
Rua Machadinho, 465
CEP 92200-440 - Canoas, RS - Brazil
E-mail: rimattiello@hotmail.com