Pulmonary function in children and adolescents with postinfectious bronchiolitis obliterans*, **

Função pulmonar de crianças e adolescentes com bronquiolite obliterante pós-infecciosa

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Abstract

Objective: To describe the pulmonary function in children and adolescents with postinfectious bronchiolitis obliterans (PIBO), as well as to evaluate potential risk factors for severe impairment of pulmonary function. **Methods:** The pulmonary function of 77 participants, aged 8-18 years, was assessed by spirometry and plethysmography. The following parameters were analyzed: FVC; FEV_1; $FEF_{25-75\%}$; FEV_1/FVC; RV; TLC; RV/TLC; intrathoracic gas volume; and specific airway resistance (sRaw). We used Poisson regression to investigate the following potential risk factors for severe impairment of pulmonary function: gender; age at first wheeze; age at diagnosis; family history of asthma; tobacco smoke exposure; length of hospital stay; and duration of mechanical ventilation. **Results:** The mean age was 13.5 years. There were pronounced decreases in FEV_1 and $FEF_{25-75\%}$, as well as increases in RV and sRaw. These alterations are characteristic of obstructive airway disease. For the parameters that were the most affected, the mean values (percentage of predicted) were as follows: FEV_1 = 45.9%; $FEF_{25-75\%}$ = 21.5%; RV = 281.1%; RV/TLC = 236.2%; and sRaw = 665.3%. None of the potential risk factors studied showed a significant association with severely impaired pulmonary function. **Conclusions:** The patients with PIBO had a common pattern of severe pulmonary function impairment, characterized by marked airway obstruction and pronounced increases in RV and sRaw. The combination of spirometric and plethysmographic measurements can be more useful for assessing functional damage, as well as in the follow-up of these patients, than are either of these techniques used in isolation. Known risk factors for respiratory diseases do not seem to be associated with severely impaired pulmonary function in PIBO.

Keywords: Respiratory function tests; Airway obstruction; Bronchiolitis obliterans.

Resumo

Objetivo: Descrever a função pulmonar de crianças e adolescentes com bronquiolite obliterante pós-infecciosa (BOPI) e avaliar potenciais fatores de risco para pior função pulmonar. **Métodos:** A função pulmonar de 77 participantes, com idades de 8-18 anos, foi avaliada por meio de espirometria e pletismografia. Os seguintes parâmetros foram analisados: CVF, VEF_1, $FEF_{25-75\%}$, VEF_1/CVF, VR, CPT, VR/CPT, volume de gás intratorácico e *specific airway resistance* (sRaw, resistência específica das vias aéreas). Foi utilizada a regressão de Poisson para investigar os seguintes potenciais fatores de risco para pior função pulmonar: sexo, idade do primeiro sibilo, idade ao diagnóstico, história familiar de asma, exposição ao tabaco, tempo de hospitalização e tempo de ventilação mecânica. **Resultados:** A idade média foi de 13,5 anos. Houve uma diminuição importante de VEF_1 e $FEF_{25-75\%}$, assim como um aumento de VR e sRaw, característicos de doença obstrutiva das vias aéreas. Os parâmetros mais afetados e as médias percentuais dos valores previstos foram VEF_1 = 45,9%; $FEF_{25-75\%}$ = 21,5%; VR = 281,1%; VR/CPT = 236,2%; e sRaw = 665,3%. Nenhum dos potenciais fatores de risco avaliados apresentou uma associação significativa com pior função pulmonar. **Conclusões:** As crianças com BOPI apresentaram um padrão comum de comprometimento grave da função pulmonar, caracterizado por uma obstrução importante das vias aéreas e um expressivo aumento de VR e sRaw. A combinação de medidas espirométricas e pletismográficas pode ser mais útil na avaliação do dano funcional, assim como no acompanhamento desses pacientes. Fatores de riscos conhecidos para doenças respiratórias não parecem estar associados a pior função pulmonar em BOPI.

Descritores: Testes de função respiratória; Obstrução das vias respiratórias; Bronquiolite obliterante.

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* Study carried out under the auspices of the Graduate Program in Pediatrics, *Universidade Federal do Rio Grande do Sul* – UFRGS, Federal University of Rio Grande do Sul – Porto Alegre, Brazil.

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Financial support: Rita Matiello is the recipient of a grant from the Brazilian *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development).
Submitted: 11 December 2009. Accepted, after review: 15 March 2010.

** A versão completa em português deste artigo está disponível em www.jornaldepneumologia.com.br

Introduction

Bronchiolitis obliterans (BO) is an uncommon form of chronic lung disease that follows a severe insult to the lower respiratory tract. From the pathological perspective, it is characterized by partial or complete luminal obstruction of the small airways by scar tissue, secondary to inflammation and fibrosis.[1,2] Because organ transplantation has improved survival in patients with lung disease patients, the incidence of BO as a manifestation of graft rejection has increased.[3] In children and adolescents, however, the most common form of BO, especially in developing countries, is postinfectious BO (PIBO).[4]

There have been reports of PIBO on most continents, interesting data coming from South American countries and corresponding to the adenovirus epidemics that occurred during the 1990s.[4-6] In PIBO, as in other chronic lung diseases, determining pulmonary function is crucial for the diagnosis, as well as for classifying the severity of the condition and monitoring its progression. Unfortunately, there is only sparse information in the literature regarding the pulmonary function of patients with PIBO. Two studies (both conducted by the same research group) evaluated pulmonary function in infants with PIBO.[5,7] Those two studies produced consistent results, since both included a representative number of patients. That is not the case for studies involving children and adolescents with PIBO; the few articles providing lung function data usually have small sample sizes and different methodology or focus, which precludes an appropriate characterization of LF.[8-11] This effectively prevents us from drawing reliable conclusions regarding the characteristics of pulmonary function in this age bracket.

Profiling the pulmonary function of children and adolescents with PIBO could give us a better insight of the long-term respiratory effects of the disease. This could be of interest not only to those studying and treating patients with PIBO, but also to those in the field of lung transplantation, since the histopathological similarities between transplant and PIBO[12] could translate to similarities in pulmonary function. The objective of this study was to describe the pulmonary function of children and adolescents with PIBO and to evaluate the potential risk factors for severe impairment of pulmonary function.

Methods

This was a cross-sectional study involving children and adolescents (8-18 years of age) with PIBO, in Brazil and Chile. The participants were periodically monitored at one of two tertiary care pediatric pulmonology outpatient clinics: that of the *Hospital da Criança Santo Antonio*, located in the city of Porto Alegre, Brazil; or that of the *Centro de Referencia de Salud del Hospital El Pino*, located in the city of Santiago, Chile. The staff at both clinics have extensive clinical experience in diagnosing and monitoring pediatric patients with PIBO, having done so for more than 15 years. For the purposes of this study, we analyzed the results of pulmonary function tests carried out in 2007. Of the 83 patients initially eligible for inclusion in the study, 5 presented with pulmonary function test results that did not meet the acceptability/reproducibility criteria of the American Thoracic Society/European Respiratory Society (ATS/ERS) and another declined to participate in the study. Those 6 patients were therefore excluded. Consequently, the final sample consisted of 77 patients: 41 in Brazil and 36 in Chile.

The criteria for a diagnosis of PIBO were based on previous reports[1,8,13,14] and included all of the following:

- acute, severe bronchiolitis/viral pneumonia during the first 3 years of life in children who had previously been healthy
- evidence of persistent airway obstruction after the acute event (identified either by physical examination or by pulmonary function testing) that was unresponsive to at least two weeks of treatment with systemic corticosteroids and bronchodilators
- chest X-ray findings indicative of chronic lung disease (e.g., hyperinflation, atelectasis, airway wall thickening, and bronchiectasis)
- mosaic pattern and air trapping on chest CT
- exclusion of other conditions that progress to permanent respiratory symptoms, including chronic lung diseases such as tuberculosis, cystic fibrosis, and bronchopulmonary dysplasia, as well as immunodeficiency and alpha-1-antitrypsin deficiency

Spirometric parameters—FVC, FEV_1, $FEF_{25-75\%}$, and FEV_1/FVC—and plethysmographic parameters—intrathoracic gas volume (ITGV),

RV, TLC, RV/TLC, and specific airway resistance (sRaw)—were measured in accordance with international recommendations for acceptability and reproducibility.[15,16] The pulmonary function parameters were measured only if patients had been free of respiratory exacerbations and clinically stable for at least two weeks. Short-acting and long-acting β_2 agonists were withheld for, respectively, 12 h and 48 h prior to the tests, although inhaled corticosteroids were maintained as prescribed. Before any tests were conducted, the patients were familiarized with the basic maneuvers for spirometric and plethysmographic measurements.

At each facility, the measurements were conducted by an accredited laboratory technician. All measurements were taken in the morning (plethysmography followed by spirometry). Both centers used the same type of spirometer (MasterScreen Body, with software, v4.3; Jaeger, Würtzburg, Germany), which was calibrated daily using a 3-L syringe, and measurements were electronically corrected to body temperature and pressure, saturated conditions.[15-17]

During the plethysmography, the patients were instructed to breathe calmly through a mouthpiece until reaching a stable end-expiratory level. The shutter then closed automatically for 2-3 s while the patients performed a series of shallow panting maneuvers (against 0.5-1.0 Hz of resistance), with both hands supporting their cheeks. The results of three to five technically satisfactory maneuvers were registered for subsequent analysis. The shutter was opened, and the patients slowly exhaled as completely as possible (to allow the expiratory reserve volume to be determined). Subsequently, the patients slowly inhaled up to TLC, and this was followed by a forced expiratory maneuver in which the patient exhaled down to RV. The effort with the greatest VC and the best shutter maneuver, which included the loop closest to the pressure-volume axis, was considered the best effort. Spirometric measurements were taken after the patient had rested for 5 min. Appropriate values were selected from the best three acceptable and reproducible FVC maneuvers, and the selected maneuver was the one with the greatest sum of FVC and FEV_1.

We employed the reference values and equations devised by Perez-Padilla et al. and Zapletal et al. for spirometry and plethysmography, respectively.[18,19] All pulmonary function data are expressed as a percentage of the predicted reference value. The severity of impairment for spirometric parameters was based on FEV_1 according to the ATS/ERS recommendations,[20] and the normality ranges accepted for volumes were those recommended by the *Sociedad Española de Neumología y Cirugía Torácica* (Spanish Society of Pulmonology and Thoracic Surgery).[21] We defined severely impaired pulmonary function as that classified as severe or very severe impairment, according to the ATS criteria.[20]

Continuous variables are expressed as mean and 95% CI, whereas categorical variables are expressed as absolute and relative frequency. The adjusted prevalence ratios of potential risk factors for severe impairment of pulmonary function were calculated by Poisson regression with robust error variance in bivariate and multivariate analyses. This was followed by an interactive procedure, initially considering all covariates with a p value < 0.10 in a multiple regression model. The covariates with the

Table 1 - Demographic data of the participants, by country.

Variable	Brazil	Chile	Both countries
	(n = 41)	(n = 36)	(n = 77)
Age,[a] years	11.5 (10.7-12.3)	15.1 (14.0-16.3)	13.3 (12.4-14.0)
Height,[a] cm	144.6 (139.7-149.5)	157.3 (152.6-162.0)	150.5 (146.9-154.1)
BMI,[a] kg/m^2	17.9 (16.9-18.9)	21.4 (20.0-22.9)	19.5 (18.6-20.5)
Age at diagnosis,[a] months	12.2 (9.6-14.6)	10.78 (8.2-13.3)	11.4 (9.7-13.2)
0-6[b]	7 (17.1)	9 (25.0)	16 (20.8)
7-12[b]	22 (53.6)	17 (47.2)	39 (50.6)
13-24[b]	10 (24.4)	9 (25.0)	19 (24.7)
>24[b]	2 (4.9)	1 (2.8)	3 (3.9)
Male gender[b]	31 (75.6)	19 (52.8)	50 (64.9)

[a]Values expressed as mean (95% CI). [b]Values expressed as n (%).

Table 2 - Pulmonary function parameters of the participants, by country.

Parameter[a]	Brazil[b]	Chile[b]	Both countries[b]
	(n = 41)	(n = 36)	(n = 77)
FVC	61.7 (56.9-66.4)	72.5 (68.2-76.8)	66.8 (63.4-70.2)
FEV_1	42.5 (37.6-47.0)	49.7 (44.7-54.8)	45.9 (42.4-49.4)
$FEF_{25-75\%}$	19.9 (16.0-23.8)	23.4 (19.1-27.7)	21.5 (18.6-24.4)
FEV_1/FVC	67.6 (63.1-72.1)	66.8 (62.5-71.1)	67.2 (64.1-70.3)
TLC	116.8 (113.1-120.5)	112.5 (10.8-117.1)	116.8 (113.2-120.5)
ITGV	162.7 (154.0-171.4)	144.5 (134.6-154.3)	162.7 (154.0-171.4)
RV	281.1 (258.6-303.7)	231.0 (203.2-258.7)	281.1 (258.6-303.7)
RV/TLC	236.2 (222.5-250.40)	200.9 (184.7-217.1)	236.2 (222.5-250.0)
sRaw	746.6 (597.5-895.7)	572.8 (431.9-713.6)	665.3 (562.5-768.2)

ITGV: intrathoracic gas volume; and sRaw: specific airway resistance. [a]Values expressed as percentage of the predicted value. [b]Values expressed as mean (95% CI).

highest p values were removed from the model, which was then recalculated. The final model comprised only covariates with a p value < 0.10. We included the following variables as potential risk factors: ggender; age at first wheeze; age at diagnosis; family history of asthma; tobacco smoke exposure; length of hospital stay; and duration of mechanical ventilation. The correlation between RV/TLC and FEV_1, as well as that between RV/TLC and $FEF_{25-75\%}$, was assessed using Pearson's correlation coefficient (r). The level of statistical significance was set at $p < 0.005$.

The study was approved by both local research ethics committees. The parents or legal guardians of the participants gave written informed consent, and the participating patients verbally agreed to be included in the study.

Results

The demographic data are shown in Table 1. In both groups, there was a predominance of males (Brazil: 75.6%; Chile: 52.8%). The overall means (and the group means for Brazil and Chile, respectively) were as follows: age, 13.3 years (11.5 and 15.1 years); height, 150.5 cm (144.6 and 157.3 cm); and BMI, 19.5 kg/m^2 (17.9 and 21.4 kg/m^2). The onset of the disease occurred between 1 and 24 months of age in most of the patients (97% of the group in Brazil and 97% of the group in Chile).

Table 2 shows the pulmonary function parameters. In both groups, the mean values of all spirometric variables, especially FEV_1 and $FEF_{25-75\%}$, were low. Correspondingly, the mean values of most plethysmographic variables (ITGV, RV, RV/TLC, and sRaw) were markedly high, with the exception of TLC, which was within normal limits.

In the regression model, none of the potential risk factors demonstrated a significant association with severely impaired pulmonary function. There was a moderate correlation between RV/TLC and FEV_1 ($r = -0.657$, $p < 0.001$) and between RV/TLC and $FEF_{25-75\%}$ ($r = -0.669$, $p < 0.001$).

Discussion

The present study describes pulmonary function in one of the largest samples of pediatric patients with PIBO evaluated to date. Our results show that, at both of the facilities involved, the children and adolescents with PIBO presented with moderate to very severe airway obstruction.[20] This impairment, which probably reflects major chronic damage of the medium and small airways, is characterized by decreased expiratory airflow, together with increased RV and sRaw.

In order to elucidate the great impact that PIBO has on the major morphological and functional components of the respiratory system, a combination of methods must be employed. One such method is pulmonary function testing, which allows us to assess, in a relatively practical and noninvasive manner that is most suitable for diagnostic and follow-up routines, how the viscoelastic and flow-resistive properties of the system are impaired.[22]

Because PIBO is a rare disease with a relatively small number of patients in any given country, the use and results of pulmonary function testing

in PIBO patients have been addressed in only a few studies, six of which have been notable:

- Studying a sample of 13 infants in Argentina, Teper et al. suggested that the functional impairment caused by PIBO is established at its early stages.[7]
- Kim et al. described the pulmonary function of 14 children within a study group of 31 children with PIBO in the USA and South Korea. The authors found that all 14 presented with severe, fixed airway obstruction.[9]
- Castro-Rodriguez et al., using the impulse oscillometry technique, found evidence of peripheral airway dysfunction in 18 preschool children in Chile.[23]
- Cazzato et al. conducted a longitudinal study of the pulmonary function of 14 children in Italy and found an annual decline of 1% in the predicted values of FEV_1, FEV_1/FVC and $FEF_{25-75\%}$.[10]
- In Brazil, Mattiello et al. assessed the functional capacity of 20 children during cardiopulmonary exercise testing and compared the results with those of conventional pulmonary function testing. The children presented with reduced oxygen consumption, which correlated positively with FVC, FEV_1, and RV/TLC.[11]
- Mattiello et al. also studied a group of 21 children in Brazil and showed that the CT findings in early life seem to predict severely impaired pulmonary function a decade later.[24]

Our results corroborate and expand upon a conclusion drawn on the basis of those studies: the functional hallmark of the disease is marked airway obstruction with air trapping. Another group of authors described PIBO patients with a restrictive or mixed pattern of obstruction.[25] However, those authors based their analysis solely on a reduced FVC that was associated with a normal or low FEV_1/FVC ratio.[25] Therefore, their finding can be explained in the context of a considerable airway obstruction that leads to pronounced air trapping, the degree of which is best determined through the assessment of lung volumes.[20] The ATS and ERS both recommend the determination of lung volumes in patients with obstructive lung diseases, such as PIBO, because it allows a better understanding of the underlying respiratory impairment.[16,20] In fact, when airflow obstruction becomes more severe as a result of decreased lung elastic recoil or changes in dynamic mechanisms, ITGV, RV, TLC, and RV/TLC tend to increase.

We found only two studies evaluating lung volumes in pediatric patients with PIBO.[9,10] We pooled the data of their collective sample (n = 25) and, disregarding any methodological differences, found that all of the patients showed a marked increase in RV. In our study sample (n = 77), we also identified patients with reduced FVC. However, in those patients, the TLC was also considerably above 80% of the predicted value, with a noticeable increase in RV and RV/TLC. These lung volume data, obtained by plethysmography, leave no doubt as to the obstructive nature of PIBO. In addition, we found that, overall, RV/TLC presented good correlations with two of the spirometric parameters, FEV_1 and $FEF_{25-75\%}$, indicating that the degree of hyperinflation paralleled the severity of airway obstruction. This situation can lead to progressive clinical consequences, such as a permanent need for oxygen therapy or impaired quality of life.

Although FEV_1/FVC and FEV_1 are the spirometric parameters most often employed in order to determine airway obstruction, $FEF_{25-75\%}$ has also been considered a relevant early indicator of this abnormality, since it appears to show a proportionately greater reduction than does FEV_1 or FEV_1/FVC.[9,10,20] Our results show that all of the patients had abnormal values for $FEF_{25-75\%}$ and FEV_1, the $FEF_{25-75\%}$ value being half of that obtained for FEV_1. This is in agreement with the current recommendations for diagnosing bronchiolitis obliterans syndrome (BOS) in transplant patients. Since $FEF_{25-75\%}$ has been found to deteriorate sooner after BOS onset than does FEV_1,[3] the criteria for early detection of BOS now include a decline in $FEF_{25-75\%}$, as well as a decrease in FEV_1.[26] Because $FEF_{25-75\%}$ presents considerable variability, as evidenced in a recent study,[27] its routine use in clinical practice has been controversial. However, its considerable and consistent reduction in our patients with PIBO suggests that $FEF_{25-75\%}$ should be considered together with the established duo of FEV_1 and FEV_1/FVC to define the extent of functional damage, as well as in the routine follow-up of such patients. The fact that it is obtained simultaneously with other spirometric

parameters and through the same technique strengthens its feasibility.

One limitation of our study is that our two groups of patients with PIBO were each from a different country. However, since both of those countries are in the southern portion of South America, there are geographic, ethnic, and nutritional similarities between the two groups. In addition, they all developed the disease at similar (young) ages, corresponding to simultaneous regional bursts of severe adenovirus respiratory infections during the early and mid 1990s.[28] Furthermore, the measurements corresponded to pulmonary function testing obtained during the same year, both pulmonary function testing laboratories are board certified, both follow the ATS/ERS recommendations, and both used the same apparatus and software. The group results are presented together with those of the sample as a whole, and it is clear that the two patient groups were similar in terms of pulmonary function.

Our sample size was adequate to run the statistical model used, and our analyses revealed that none of the factors studied constituted a risk for severe impairment of pulmonary function.

We believe that the value of our study lies in the large number of participants and the broad age range of the sample, as well as in the use and analysis of an extensive number of pulmonary function variables. These aspects allowed us to obtain data that are consistent and reliable. Our data can inform decisions regarding the evaluation and treatment of patients with PIBO, as well as those regarding future studies in children or adolescents with post-transplant BO.

In conclusion, pediatric patients with PIBO have a common pattern of severe pulmonary function impairment, characterized by marked airway obstruction and a pronounced increase in RV and sRaw. Our results suggest that the combined use of spirometric and plethysmographic measurements is more useful than is that of each method alone in assessing functional damage at a given time and in the follow-up of children or adolescents suffering from this rare disease.

Acknowledgments

The authors wish to thank Dr. Sonia Buist and Dr. Gordon Rubenfeld, both of whom are professors for the ATS-MECOR Course (http://www.thoracic.org/global-health/mecor-courses/mecor-program-description.pdf), for their support and suggestions regarding this manuscript.

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