Pulmonary function parameters and use of bronchodilators in patients with cystic fibrosis*

Características funcionais pulmonares e uso de broncodilatador em pacientes com fibrose cística

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Abstract

Objective: To analyze pulmonary function parameters and pharmacodynamic response to a bronchodilator, as well as the prescription of bronchodilators, in cystic fibrosis (CF) patients. **Methods:** This was a retrospective cohort study involving patients 6-18 years of age, diagnosed with CF, and followed at a referral center between 2008 and 2010. We evaluated only those patients who were able to perform pulmonary function tests (PFTs). We analyzed FVC, FEV_1, and $FEF_{25-75\%}$, expressed as percentages of the predicted values, prior to and after bronchodilator tests (pre-BD and post-BD, respectively), in 312 PFTs. Repeated measures ANOVA and multiple comparisons were used. **Results:** The study included 56 patients, divided into two groups: those whose PFT results spanned the 2008-2010 period (n = 37); and those whose PFT results spanned only the 2009-2010 period (n = 19). In the 2008-2010 group, there were significant reductions in post-BD FEV_1 between 2008 and 2010 (p = 0.028) and between 2009 and 2010 (p = 0.036), as was also the case for pre-BD and post-BD $FEF_{25-75\%}$ in all multiple comparisons (2008 vs. 2009; 2008 vs. 2010; and 2009 vs. 2010). In the 2009-2010 group, there were no significant differences between any of the years for any of the variables studied. Among the 312 PFTs, significant responses to the bronchodilator occurred in only 24 (7.7%), all of which were from patients for whom no bronchodilator had been prescribed during the study period. **Conclusions:** In the CF patients studied, there was loss of pulmonary function, indicating progressive lung disease, over time. The changes were greater for $FEF_{25-75\%}$ than for the other variables, which suggests the initial involvement of small airways.

Keywords: Cystic fibrosis; Respiratory function tests; Bronchodilator agents.

Resumo

Objetivo: Analisar as características funcionais pulmonares, a resposta farmacodinâmica a um broncodilatador e sua prescrição em pacientes com diagnóstico de fibrose cística (FC). **Métodos:** Estudo de coorte retrospectivo de pacientes (6-18 anos) com diagnóstico de FC acompanhados em um centro de referência, capazes de realizar testes de função pulmonar (TFP) entre 2008 e 2010. Foram analisados CVF, VEF_1 e $FEF_{25-75\%}$, em percentual do previsto, antes e após prova broncodilatadora (pré-BD e pós-BD, respectivamente) de 312 TFP. Foram realizadas ANOVA para medidas repetidas e comparações múltiplas. **Resultados:** Foram incluídos no estudo 56 pacientes. Desses, 37 e 19, respectivamente, tinham resultados de TFP entre 2008 e 2010 e apenas em 2009-2010, formando dois grupos. No grupo com TFP nos três anos estudados, houve redução significativa em VEF_1 pós-BD em 2008-2010 (p = 0,028) e 2009-2010 (p = 0,036) e em $FEF_{25-75\%}$ pré-BD e pós-BD em todas as comparações múltiplas (2008 vs. 2009; 2008 vs. 2010; e 2009 vs. 2010). No grupo com TFP apenas em 2009-2010, não houve diferenças significativas em nenhuma das comparações das variáveis estudadas. Dos 312 TFP, somente 24 (7,7%) apresentaram resposta significativa ao broncodilatador e pertenciam a pacientes sem prescrição de broncodilatador durante o período estudado. **Conclusões:** Houve perda funcional, com indicação de doença pulmonar progressiva, nos pacientes com FC estudados. Houve maiores alterações no $FEF_{25-75\%}$, sugerindo o comprometimento inicial de vias aéreas menores.

Descritores: Fibrose cística; Testes de função respiratória; Broncodilatadores.

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Financial support: None.
Submitted: 2 July 2012. Accepted, after review: 16 November 2012.

Introduction

Cystic fibrosis (CF) is an autosomal recessive genetic disease, and obstructive lung disease is the leading cause of morbidity and mortality in CF patients. The literature shows that children with CF are born with histopathologically normal lungs; however, peripheral airway obstruction, with retention of secretions, can be seen after the first weeks of life, followed by progressive impairment of large airways, in which mucoid impaction, chronic infection, and inflammation result in a cycle of tissue damage that is accompanied by bronchiectasis, culminating in respiratory failure.[1-4]

Pulmonary function tests (PFTs) are useful in assessing lung disease severity and progression. Lung disease in CF patients is essentially obstructive. There is limited evidence of improvement in pulmonary function in CF patients with the use of inhaled bronchodilators, and PFT results vary (improvement, worsening, or no change).[5,6]

The objective of the present study was to analyze pulmonary function parameters and pharmacodynamic (bronchodilator) response, as well as the prescription of bronchodilators, in CF patients treated at a referral center in Brazil.

Methods

This was a retrospective cohort study involving children and adolescents with CF followed at the Cystic Fibrosis Referral Center of the *Irmandade da Santa Casa de Misericórdia de São Paulo*, located in the city of São Paulo, Brazil, between January of 2008 and December of 2010. The present study was approved by the Research Ethics Committee of the *Irmandade de Ciências Médicas da Santa Casa de São Paulo* (Protocol no. 224/11).

The study included patients between 6 and 18 years of age who were able to perform PFTs during the study period and excluded those who were transferred to other treatment centers, those who died, and those who were not able to perform PFTs in accordance with the acceptability and reproducibility criteria set forth by Brazilian guidelines.[7] Clinical data and data from PFTs combined with pharmacodynamic testing were abstracted from the outpatient medical records of participants.

Pulmonary function was assessed by spirometry, which was performed at the Pulmonary Function Testing Laboratory of the hospital. All PFTs were supervised by the same well-trained technician, and participants wore a nose clip. For the tests, a Koko spirometer (PDS Instrumentation, Inc., Louisville, CO, USA) with a pneumotachograph was connected to a computer.

Spirometry tests were performed, and volume-time and flow-volume curves were measured. The environment in which the tests were performed was calm and private, and temperature and humidity were kept constant. Pharmacodynamic testing was performed with albuterol aerosol, at a dose of 400 µg. The volume-time and flow-volume curves should meet the acceptability and reproducibility criteria set forth by Brazilian guidelines,[7] as well as the criteria for a significant bronchodilator response.[8] The FVC, FEV_1, and $FEF_{25-75\%}$ values were derived from these curves, and the predicted values used were those of Polgar & Promadhat.[9]

We selected spirometry tests performed on an outpatient basis, when patients experienced no exacerbation of lung disease. The outpatient prescription of bronchodilators occurring outside the period of hospitalization was considered.

In the statistical analysis, repeated measures ANOVA was used for the comparison of the mean FVC, FEV_1, and $FEF_{25-75\%}$ values (expressed as percentages of the predicted values) in 2008, 2009, and 2010. The Student's t-test for paired samples was used for the comparison of the mean FVC, FEV_1, and $FEF_{25-75\%}$ values (expressed as percentages of the predicted values) in 2009 and 2010 and for multiple comparisons. For all tests, the level of significance was set at 5%.

Results

Of the 67 patients initially included in the study, 7 were not able to perform PFTs, 2 died, and 2 were transferred to another state. The final sample consisted of 56 patients.

The median age of participants at the end of the study period was 11.1 years (range, 7.3-19.4 years), and the median age at diagnosis was 2.4 years (range, 0.1-13.7 years). Of the 56 patients, 30 (53.6%) were female.

We evaluated 312 PFTs performed by the 56 selected patients during the study period. Each patient contributed at least two and at most ten spirometry tests.

For the purpose of analyzing the PFTs, the patients were divided into two groups: those whose PFT results spanned the 2008-2010 period (n = 37); and those whose PFT results spanned only the 2009-2010 period (n = 19).

In the 2008-2010 group, 254 PFTs were analyzed.

A mean FVC (expressed as a percentage of the predicted value—FVC%) profile analysis in the 2008-2010 group over the three years studied showed no statistically significant variations in the values obtained prior to bronchodilator tests ((pre-BD) or in those obtained after bronchodilator tests (post-BD; Figure 1). In this same group, a mean pre-BD FEV_1 (expressed as a percentage of the predicted value—FEV_1%) profile analysis over the three years studied showed no statistically significant differences (p = 0.060). However, a mean post-BD FEV_1% profile analysis showed a statistically significant decrease (p = 0.038; Figure 2). A multiple comparison analysis showed that the decrease in post-BD FEV_1% values was significant in the 2008-2010 period and in the 2009-2010 period (p = 0.028 and p = 0.036, respectively; Table 1). Also in this group, a mean $FEF_{25-75\%}$ (expressed as a percentage of the predicted value—$FEF_{25-75\%}$%) profile analysis over the three years studied showed a statistically significant reduction in pre-BD and post-BD values (p < 0.001 for both; Figure 3), and a multiple comparison analysis showed that the annual variations in the 2008-2010 period were significant (Table 1).

The analysis of the remaining 58 PFTs, all of which were from the 19 patients in the 2009-2010 group, showed no statistically significant

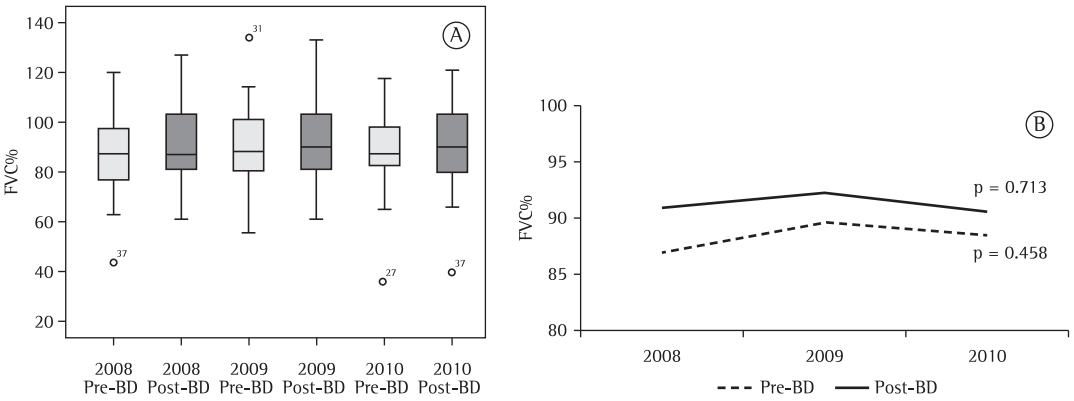

Figure 1 - In A, box plot analysis of FVC expressed as a percentage of the predicted value (FVC%), prior to and after bronchodilator tests (pre-BD and post-BD, respectively), in 37 cystic fibrosis patients whose pulmonary function test results spanned the 2008-2010 period. In B, mean pre-BD and post-BD FVC% profile for the years studied and the p values (ANOVA).

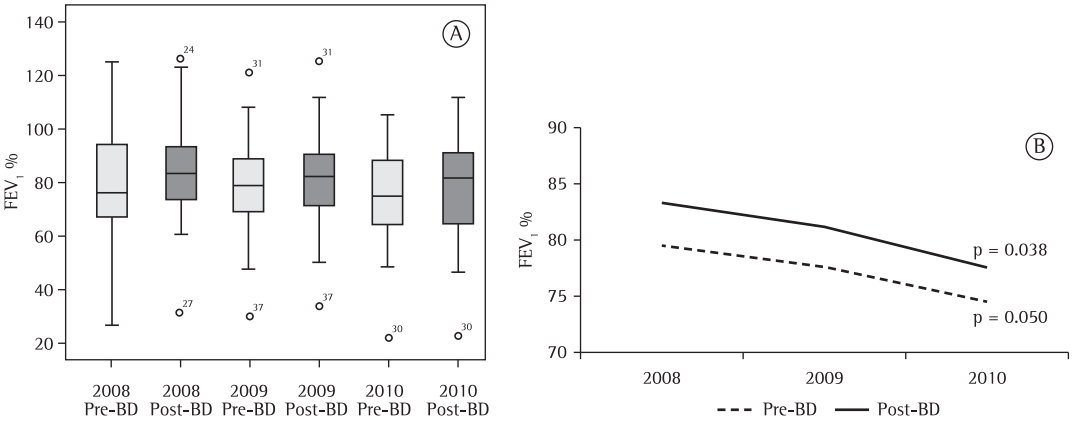

Figure 2 - In A, box plot analysis of FEV_1 expressed as a percentage of the predicted value (FEV_1%), prior to and after bronchodilator tests (pre-BD and post-BD, respectively), in 37 cystic fibrosis patients whose pulmonary function test results spanned the 2008-2010 period. In B, mean pre-BD and post-BD

variations in pre-BD or post-BD values for any of the three parameters studied (Table 2).

The occurrence of a significant bronchodilator response in the PFTs was determined with the following formulas:

(post-BD FEV_1% – pre-BD FEV_1%) × 100/ FEV_1% predicted > 7%

(post-BD FEV_1% – pre-BD FEV_1%) ≥ 200 mL

This analysis showed that, among the 312 PFTs, a significant bronchodilator response occurred in 24 (7.7%).

Over the three years studied, we found that, of the total sample of 56 patients, 7 had been prescribed bronchodilator treatment on the basis of clinical recommendation but had no significant bronchodilator response, as shown by their PFT results during the study period, whereas 18 patients, who had had no clinical

Table 1 - Analysis of variations in mean FEV_1 expressed as a percentage of the predicted value (after bronchodilator tests) and in mean $FEF_{25-75\%}$ expressed as a percentage of the predicted value (prior to and after bronchodilator tests) in 37 cystic fibrosis patients whose pulmonary function test results spanned the 2008-2010 period.

Post-BD FEV_1 expressed as a percentage of the predicted value*	
Multiple comparisons	p
2008-2009	0.335
2008-2010	0.028
2009-2010	0.036
Pre-BD $FEF_{25-75\%}$ expressed as a percentage of the predicted value**	
Multiple comparisons	p
2008-2009	0.006
2008-2010	< 0.001
2009-2010	< 0.003
Post- BD $FEF_{25-75\%}$ expressed as a percentage of the predicted value**	
Multiple comparisons	p
2008-2009	0.013
2008-2010	< 0.001
2009-2010	< 0.001

Post-BD: after bronchodilator tests; and pre-BD: prior to bronchodilator tests. *p = 0.038; repeated measures ANOVA. **p < 0.001; repeated measures ANOVA.

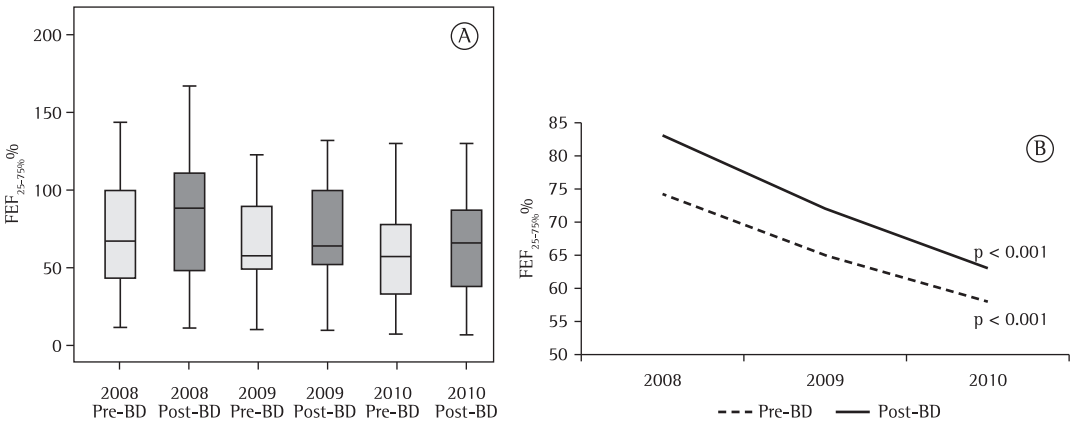

Figure 3 - In A, box plot analysis of $FEF_{25-75\%}$ expressed as a percentage of the predicted value ($FEF_{25-75\%}$%), prior to and after bronchodilator tests (pre-BD and post-BD, respectively), in 37 cystic fibrosis patients whose pulmonary function test results spanned the 2008-2010 period. In B, mean pre-BD and post-BD $FEF_{25-75\%}$% profile for the years studied and the p values (ANOVA).

Table 2 - Analysis of variations in mean FVC, FEV_1, and $FEF_{25-75\%}$ values, expressed as percentages of the predicted values, prior to and after bronchodilator tests, in 19 cystic fibrosis patients whose pulmonary function test results spanned only the 2009-2010 period.*

Year	FVC, % of predicted		p
2009	Pre-BD	74.9	0.108
	Post-BD	77.8	
2010	Pre-BD	69.4	0.716
	Post-BD	76.4	
	FEV_1, % of predicted		
2009	Pre-BD	59.5	0.138
	Post-BD	62.9	
2010	Pre-BD	55.3	0.635
	Post-BD	61.1	
	$FEF_{25-75\%}$, % of predicted		
2009	Pre-BD	38.9	0.311
	Post-BD	44.5	
2010	Pre-BD	36.1	0.415
	Post-BD	41.3	

Pre-BD: prior to bronchodilator tests; and post-BD: after bronchodilator tests. *Student's t-test.

need to be prescribed bronchodilators during the study period, had the tests that revealed a significant bronchodilator response.

Discussion

In the present study, we analyzed data on 56 CF patients regularly followed at a referral center over a three-year period (2008-2010). We assessed pulmonary function parameters, pharmacodynamic (bronchodilator) response, and the prescription of bronchodilators.

The analysis of the spirometry parameters during the three-year follow-up period showed that the mean FVC% did not vary significantly, with values being within the normal range.

The mean pre-BD FEV_1% profile analysis showed no significant variations, whereas the mean post-BD FEV_1% profile analysis revealed a trend toward a decrease, the limitation of which was likely due to the sample size. We found that the mean values were already below the normal range for FEV_1%, with progressive worsening over the study period. Although the mean post-BD FEV_1% analysis showed an increase in values, there was a decrease to values below the normal range over the study period, with significant variations in three years.

The mean pre-BD and post-BD $FEF_{25-75\%}$% profile showed the most significant reductions over the study period and at each year studied.

The analysis of the group of patients whose PFT results spanned a two-year period showed no significant decreases in any of the three parameters studied.

The two study groups were formed as follows: patients whose PFT results spanned a two-year period; and patients whose PFT results spanned a three-year period. Because this study was a retrospective analysis, it was not possible to establish the frequency of the tests or to monitor the groups.

It is of note that the present study, conducted over a three-year period and involving children and adolescents between 6 and 18 years of age, reported significantly declining spirometry curves. It should be emphasized that the study sample consisted of patients whose median age at the end of the study period was 11.1 years and whose median age at diagnosis was 2.4 years, with high variability within this range. This might be due to the fact that newborn screening for CF was implemented in the state of São Paulo only in 2010, and the absence of such screening might have hindered early diagnosis and treatment in the study population.

The post-BD spirometry parameters studied (FVC%, FEV_1%, and $FEF_{25-75\%}$%) improved. However, a significant bronchodilator response occurred in only a few tests (7.7%). It is noteworthy that only a few patients had been prescribed bronchodilators on the basis of clinical recommendation during the study period, although the analysis of the respective spirometry test results showed no significant bronchodilator response. The tests that revealed a significant bronchodilator response were from patients who had had no clinical symptoms requiring the use of bronchodilators during the study period.

Progressive changes in pulmonary function were described in a multicenter study involving 18,411 CF patients in Canada and the USA between 1993 and 1995.[10] The patients were divided into two age groups: 6 to 12 years (children) and 13 to 17 years (adolescents). The mean FVC% values for the children and adolescents were, respectively, > 90% of predicted and 80-90% of predicted, whereas the mean FEV_1% values were, respectively, 85-90% of predicted and 75-80% of predicted. The mean $FEF_{25-75\%}$% values showed

an earlier decline in the children, being close to 70% of predicted, and were as low as 50% of predicted in the adolescents.

One study[11] involving 52 CF patients followed at a referral center in the city of Porto Alegre, Brazil, demonstrated that there was progressive change in pulmonary function, with FVC% values remaining above normal until the age of 18 years, FEV_1% values being below 80% of predicted at the age of 10 years and reaching 50% of predicted at the age of 18 years, and $FEF_{25-75\%}$% being as low as 19% of predicted at the age of 18 years.

A multicenter study,[12] conducted between 1994 and 2005 in the USA and involving 20,644 CF patients between 6 and 45 years of age, found that there were year-to-year changes in FEV_1, with maximal decreases occurring in 14-15 year olds.

Patients with CF have shown varying bronchodilator response over time, and the mechanisms involved have yet to be fully understood. There is little evidence to support the long-term use of bronchodilators in such patients.[13]

The use of bronchodilators to treat lung disease in CF patients has been quite controversial, although bronchodilators are widely prescribed. A study conducted between 1995 and 2005[14] found that the use of bronchodilators increased from 72% in 1995 to 84% in 2005.

Airway obstruction in CF patients occurs primarily by accumulation of secretions. Although cough is one of the most common symptoms of lung disease, wheezing is a frequently reported symptom. The onset of action of bronchodilators in the airways to reverse bronchospasm does not always occur in CF patients. The paradoxical deterioration in lung function parameters can be explained by the bronchiectasis-related phenomenon of collapse of damaged airways, which require the maintenance of smooth muscle tone in order to remain patent.

The lack of a bronchodilator response or a negative response at certain time periods might be due to increased retention of secretions, edema of the airway mucosa causing receptor hyporesponsiveness, failure to mobilize secretions, or mobilization of secretions from the small airways leading to obstruction of the large airways.

Some authors believe that beta-agonists have the effect of mucociliary clearance, increasing hydration and mucus secretion, and therefore improving pulmonary function.[15-17]

One group of authors[18] demonstrated that CF patients have unstable airways and that differences in expiratory flow can cause changes in bronchomotor tone. Airway instability would cause not only airway distension during inhalation, but increased compression during forced exhalation, and the use of bronchodilators can lead to an increase in large airways collapse.

In a study involving children and adults with CF,[19] it was suggested that bronchial lability is more severe in patients with more advanced lung disease. Methacholine responders had more severe lung disease, with lower Shwachman-Kulczycki scores and greater losses of pulmonary function. According to that study, bronchial reactivity could be secondary to bronchial injury, suggesting different pathophysiological approaches in CF and in asthma.

Wheezing is a commonly reported symptom in CF patients, and, in some cases, it is due to concomitant asthma.[20]

The triad of asthma, rhinitis, and atopic dermatitis is present in 8-25% of the world's population, and the increase in its prevalence in recent years has accompanied the increase in the prevalence of asthma.[21] However, there is no consensus regarding the definition of the asthma profile in CF patients that requires bronchodilator treatment. Airway obstruction (which is reversible with bronchodilator use), seasonality, induction by allergens, a personal history of atopy (eczema or rhinitis), and a family history of asthma can be useful as predictors of asthma.[22]

Studies involving the use of bronchodilators in CF patients have shown varying PFT results (improvement, worsening, or no change).[6,15,18,23-28]

Pattishall,[23] analyzing data from 573 PFTs performed by 127 CF patients between 1980 and 1988, observed a lack of intra-individual consistency in bronchodilator response, finding, among patients with a negative bronchodilator response, results of a positive bronchodilator response at some time during the study period.

Review studies have demonstrated the effectiveness of the use of inhaled bronchodilators, especially in individuals with evidence of bronchial hyperreactivity and bronchodilator responsiveness. However, controversy still surrounds the use of these variables to diagnose asthma in CF patients.

A European consensus statement on the treatment of lung disease in CF has established that bronchodilators should be used in the presence of persistent wheezing or exercise-induced bronchospasm in CF patients who experience symptom relief with the treatment (grade of recommendation D) and that bronchodilators should be used before the administration of inhaled antibiotics or hypertonic saline (grade of recommendation B).[29]

The present study corroborates previous reports in the literature in that CF patients experience progressive loss of pulmonary function, with a predominance of obstructive lung disease and with reduced end-expiratory flows, suggesting early involvement of the small airways and late impairment of FVC. However, further studies are needed to confirm these findings. A significant bronchodilator response occurred in only a few tests.

Given the great variability in bronchodilator response described in the literature and the fact that respiratory symptoms are common in CF patients, spirometry tests can be useful in providing additional information on a case-by-case basis during the course of disease and during the assessment of the proposed treatment.

Chronic and progressive in course, CF is a disease whose treatment protocol includes multiple therapies. The cornerstones of treatment are pulmonary stabilization and maintenance of the quality of life.

In recent decades, there has been significant investment in inhaled therapies. This has improved survival in CF patients. However, it has led to an increased need for dedication and time devoted to treatment, causing an impact on treatment adherence, which is essential for disease control.

Evaluation of the need for bronchodilators on a case-by-case basis can slightly attenuate the exhausting daily routine of CF patients, as well as improving their quality of life and their adherence to this continuous treatment.

In conclusion, in the CF patients studied, there was loss of pulmonary function, indicating progressive lung disease, over time. The greatest changes occurred in $FEF_{25-75\%}$, which suggests early involvement of the small airways. A significant bronchodilator response occurred in only a few PFTs, all of which were from patients who had had no clinical need to be prescribed bronchodilators during the study period. The present study underscores the importance of early diagnosis and appropriate treatment of CF in making it possible to slow disease progression.

Acknowledgments

We would like to thank the *Santa Casa de São Paulo* School of Medical Sciences and the *Irmandade da Santa Casa de Misericórdia de São Paulo*.

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