Bronchodilator Responsiveness in Cystic Fibrosis Children Treated for Pulmonary Exacerbations

Mordechai Pollak[1], Michelle Shaw[1], David Wilson[1], Melinda Solomon[1], Felix Ratjen[1], and Hartmut Grasemann[1]

[1]The Hospital for Sick Children

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Abstract

Background: Cystic fibrosis (CF) pulmonary exacerbations (PEx) are associated with significant drop in pulmonary function. The clinical value of measuring bronchodilator (BD) responsiveness during treatment for PEx to monitor or predict recovery of lung function is unclear. Methods: A retrospective analysis of spirometry with BD response testing obtained during hospital admissions for PEx in pediatric CF patients. Repeated events were included for patients with BD testing during multiple admissions. Results: 249 spirometries with BD testing in 102 patients were completed around day 7 (day 4-10) of hospital admission for treatment of CF PEx. Median (IQR) forced expiratory volume in one second (FEV1) was 70.6% predicted (58.1, 84.6) prior to the PEx event (best FEV1 in 6 months prior to admission), 54.4% (41.5, 66.9) at admission, 62.3% (48.4, 74.7) around day 7 of admission and 67.1% predicted (53.8, 78.2) at end of treatment. BD response around day 7 correlated poorly with FEV1 prior to PEx (r=-0.16, p=0.02), and did not correlate with recovery to baseline FEV1 at end of treatment (r=0.08, p=0.22). Only 23/249 (9%) patients had a BD response of [?]12 % and 200 ml. BD response was not related to age or severity of lung disease and led to an immediate change in clinical management in only 4 cases. CONCLUSIONS: BD response in CF patients treated for PEx is poorly correlated with baseline pulmonary function and does not correlate with recovery of FEV1 with treatment. These data suggest that routine testing for BD response is not indicated during PEx.

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Mordechai Pollak MD, MSc[1], Michelle Shaw MSc[2], David Wilson BSc[1], Melinda Solomon MD[1], Felix Ratjen MD, PhD[1,2], Hartmut Grasemann MD[1,2]

[1]Division of Respiratory Medicine, Department of Paediatrics, Hospital for Sick Children, Toronto, ON, Canada, [2]Translational Medicine, Research Institute, Hospital for Sick Children, Toronto, ON, Canada.

Address for Correspondence:

Hartmut Grasemann, MD

Professor, Paediatrics

Division of Respiratory Medicine, Department of Paediatrics, and

Senior Associate Scientist, Research Institute

The Hospital for Sick Children and

University of Toronto

555 University Ave | Toronto, Ontario, M5G 1X8 Canada

Phone: 416 813 7654 ext 201680

Fax: 416 813 6246

E-mail: hartmut.grasemann@sickkids.ca

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A retrospective analysis of spirometry with BD response testing obtained during hospital admissions for PEx in pediatric CF patients. Repeated events were included for patients with BD testing during multiple admissions.

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CONCLUSIONS :

BD response in CF patients treated for PEx is poorly correlated with baseline pulmonary function and does not correlate with recovery of FEV_1 with treatment. These data suggest that routine testing for BD response is not indicated during PEx.

Introduction:

Pulmonary function testing (PFT) and specifically forced expiratory volume in one second (FEV_1) is commonly used to monitor lung disease progression and pulmonary exacerbations (PEx) in patients with cystic fibrosis (CF)[1]. While CF patients tend to have non-reversible obstructive patterns on PFTs[2], reversible obstruction is not uncommon[3]. Improvement in FEV_1 after inhalation of bronchodilator (BD) in individuals with CF can be attributed to bronchodilation, improved mucociliary clearance[4–6] and potentially due to directly modulating function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein[7–9]. It can be speculated that for some individuals with CF, bronchial hyperresponsiveness or asthma can also contribute to a reversible pattern of airways obstruction[10,11].

A recent American Thoracic Society (ATS)/ European Respiratory Society (ERS) statement proposed that initial spirometry testing in obstructive airway diseases should include post BD assessment, and for follow-up tests, the need for BD testing should be assessed clinically[12]. BD responsiveness is a major characteristic of asthma, and positive acute response to BD defined as a 12% or greater increase in FEV_1 helps to confirm this diagnosis[13]. Although common in CF as well, the role of assessing BD responsiveness in different disease settings remains unclear. Levine et. al. showed that BD response measured in clinically stable CF patients did not correlate with markers of atopy or clinical severity, and overall was of limited value[3]. We previously demonstrated in pediatric patients with CF that BD testing does not assist in differentiating allergic bronchopulmonary aspergillosis (ABPA) from other causes of worsening of lung function[14]. Lung function is often monitored during PEx to evaluate objectively whether patients respond to treatment. In this study we aimed to assess the clinical value of BD testing performed during hospital admission for treatment of PEx. Specifically, we aimed to assess the correlation of BD response with severity of lung disease prior to

PEx and the recovery from PEx. We also aimed to assess whether CF patients with significant BD response have distinguishable characteristics from those without BD response.

Methods:

This is a single center retrospective analysis of all patients who were admitted to the Hospital for Sick Children for treatment of CF PEx between January 2009 and December 2019, who had acceptable pulmonary function testing with BD response assessed on day 7 ± 3 days of admission. Multiple events for patients with BD testing during different admissions were included in the analysis. This study was approved by the Hospital for Sick Children Research Ethics Board (REB # 1000063663).

Patients were identified using the Toronto CF data base (REB # 1000004851). Baseline characteristics (age, gender, ethnicity, CFTR mutation, BMI, use of inhaled steroids) as well as pulmonary function test results and airway microbiology results were obtained; additionally, clinical charts were reviewed to detect any changes in management that were based on the results of BD response testing.

Spirometry testing was performed by certified and experienced technicians using VMax TM Encore systems - Carefusion, Yorba Linda, CA, USA. All results were acceptable and reproducible meeting ATS/ ERS criteria[15]. Results were transformed to percent predicted values using the global lung initiative (GLI) equations[16]. Patients were asked to refrain from any use of inhaled short acting beta agonists (SABA) for at least 4 hours and inhaled long acting beta agonists (LABA) for at least 12 hours prior to BD response testing. Spirometry and BD response testing was performed in accordance with published ATS/ERS guidelines[15].

All statistical analyses were performed in Stata 16.1 (StataCorp, College Station, TX). Quantitative data were expressed as median and interquartile range (IQR), whereas qualitative data were shown as frequencies and percentages. Correlations between outcomes were assessed using Pearson correlation coefficients. Comparison of categorical variables were calculated using Fisher's exact test and Mann-Whitney test was used for nonparametric variables. All statistical tests were two-tailed, and the significance level was 95%.

Results:

Between 2009 and 2019, 249 spirometry tests with bronchodilator response were reported for 102 patients during days 4-10 of admission for PEx. 46 patients had one admission with BD testing, 22 patients had 2 tests, and 34 had 3 or more tests. The median (IQR) of tests per patient was 2 (1,3). Median (IQR) age at BD response testing was 14.3 (11.7, 16.2) years. Additional characteristics of the study population are described in Table 1. The characteristics where not significantly different looking exclusively at the first admission with BD response testing (Table 1). Medians (IQR) of FEV_1 at baseline (best FEV_1 over 6 months prior to admission), at admission, at day 4-10 (prior to bronchodilators) and at end of treatment are presented in Table 2.

The median (IQR) (range) absolute change in FEV_1 from pre to post BD testing was 0.064 liters (0.018, 0.124) (-0.217, 0.496). The median (IQR) (range) of relative percent change in FEV_1 from pre to post BD was 4.3% (1.4, 7.8%) (-13.7, 44.2%) (Figure 1). The relative change in FEV_1 from pre to post BD was not different when comparing those prescribed inhaled steroids (ICS) (n=104/249) to those not prescribed ICS (4.9% (1.8, 7.3%), 4.1% (1.0, 7.9%); p=0.58). A total of 23/249 (9%) tests in 17/102 (17%) patients resulted in significant BD responses as defined by ATS/ERS guidelines (12% or greater change with increase of 200 ml or more in FEV_1)[15]. Significant BD response remained rare (33/249, 13%) also when defining BD response using a 12% change without the need for 200 ml increase.

To assess whether the proportion of patients with significant BD response was different from what is observed in an outpatient setting, we analysed all PFTs of CF patients who underwent BD response testing in our center as outpatients in the same time period (2009 to 2019). 2544 BD tests were performed on a total of 319 outpatient children with CF. Of these 240 (9.4%) showed a significant BD response according to ATS/ERS criteria.

Patients with significant BD response did not differ from those without, in terms of gender, ethnicity, CFTR

mutation class, use of ICS, pathogens detected in airway cultures, age, BMI or baseline FEV_1 (table 1). There was no significant difference in the proportion of patients with at least 90 % recovery to baseline after treatment, between those with a significand BD response and those without (table 1).

The relative change in FEV_1 from pre to post BD was poorly correlated to the severity of lung disease as indicated by baseline pulmonary function (r=-0.16, p=0.02) (Figure 2). Similarly, a poor correlation was seen between the relative change in FEV_1 from pre to post BD around day 7 and the recovery of FEV_1 from admission to end of treatment (r=0.14, p=0.03) (Figure 3). The change in FEV_1 from pre to post BD around day 7 did not correlate with recovery to baseline as estimated by end of treatment FEV_1 divided by the best FEV_1 in 6 months prior to admission (R = 0.08, p=0.22) (Figure 4).

Further investigating the subgroup of patients with a significant BD response, we reviewed their clinical charts to detect if any change in clinical management was initiated as a result of the BD test results. Of 17 patients with a total of 23 events, two were initiated on ICS therapy, and another two on combination ICS / long acting beta agonist (LABA) medications. For the majority of patients (13/17, 76.5%) no immediate change in management was encountered.

Discussion :

The goal of this study was to summarize the results and to review the clinical value of BD response testing in children treated for a CF PEx at the Hospital for Sick Children between 2009 and 2019. We found changes from pre to post bronchodilator FEV_1 to be generally low, and a significant BD response in this setting, as defined by ATS/ERS criteria, was a rare finding. We did not identify any significant differences in patient characteristics between the group of responders versus non responders. Furthermore, only 4/17 patients from the responders group encountered an immediate change in management as a result of the significant BD response. Furthermore, BD response poorly correlated with baseline pulmonary function prior to admission, or with percent recovery in FEV_1 from initiation to end of treatment. No correlation was found between BD response and recovery to baseline FEV_1 and the proportion of patients recovering to at least 90% of baseline FEV_1 was similar in both the BD responder and non-responder groups. Overall, BD testing appears to be of limited clinical value in this setting.

Although airway reactivity does exist in individuals with CF, the pathophysiology and the frequency of this phenomenon in the CF population is an area of controversy. Historically, Mellis and Levison showed that CF patients with lower lung function were more likely to have a positive histamine challenge test[17]. They concluded that the heightened bronchial reactivity in patients with CF reflects the severity of their underlying lung disease rather than an underlying asthmatic component. Eggleston et al. showed that CF patients with positive methacholine challenge tests, suffered from more frequent PEx and experienced a more rapid decline in FEV_1 over time compared to patients with negative methacholine challenges[18]. Comparing CF to asthma, Mitchel et al. showed that only 51% of CF patients had a positive methacholine challenge test compared to 98% of asthmatic patients. The latter had different dose–response curves and time courses, suggesting different, or disease specific pathophysiologic mechanisms leading to a positive BD response[19]. In a more contemporary study, Levin et al. showed that in clinically stable patients with CF, BD response was not associated with more severe lung disease as indicated by FEV_1<40% of predicted[3]. Notably, many changes in CF standard of care have been implemented over the years possibly explaining differences between older and more recent studies.

The proportion of patients with a significant BD response in our study was low (23/249, 9%), similar to pediatric patients tested in the ambulatory setting 240/2544 (9.4%), and using a more sensitive definition for BD response i.e., 12% without the need of 200 ml change, the proportion of responders was not largely different (33/249, 13%). On a cellular level, it has been shown that inflammation can cause impairment of β adrenergic-induced relaxation of CF airway smooth muscle[20]. However, many factors can lead to a discrepancy between in vivo and in vitro findings, and the fact that we did not quantify inflammatory markers in the airways of the patients included in our analysis limits the ability to properly investigate the influence of inflammation on airway responsiveness. Moreover, while PEx is most probably associated with

increased inflammation, these patients also received intravenous antibiotic therapy, and there may have been higher adherence to mucus clearance therapies including physiotherapy during the time of admission. It is possible that some of these circumstances impact lung function changes after bronchodilator inhalation.

Interestingly, the proportion of patients with significant BD response in this study, is significantly lower compared to the 39% reported by Levin et al. in clinically stable patients[3]. However, in that study, information is given only for the fraction of patients with significant BD response, and the proportion of test events with significant BD response is not reported. In an analysis of BD tests for outpatients seen at our CF clinic over the same time period of this study, we found the rate of significant BD response to be 240/2544 (9.4%). Overall, we found that at our center, the proportion of significant BD response tests was similar for out and inpatients.

Inhaled corticosteroid (ICS) therapy is not considered a routine for CF patients, and can be safely discontinued in most patients[21,22]. Despite that, 42% of the patients in this study were treated with ICS. This is similar to the 40% seen in the CF Foundation patient registry[23]. Interestingly, there was no difference in the proportion of patients receiving ICS in the responder group compared with the non-responders, nor was there a significant difference in BD response for those receiving ICS compared with those not receiving ICS. This suggests that the possibility of ICS masking BD response in treated CF patients is less likely, although adherence to ICS treatment was not monitored in this study. We also found that in only 4 cases, the finding of significant BD response during the admission resulted in addition of ICS or ICS + LABA, medications typically used to treat asthma.

We found no significant relationship between airway microbiology results upon admission and BD response. Aspergillus is a common pathogen in CF airways, and known to cause ABPA in up to 9% of children with CF[24]. Despite the fact that most CF patients with positive aspergillus cultures will not develop ABPA, the finding that there was no increase in BD responsiveness in aspergillus positive patients treated for PEx is in keeping with our recent finding that patients with diagnosed ABPA did not tend to have higher rates of BD responses compared to other causes of deterioration in lung function[14].

To our knowledge, this is the first study to investigate BD responsiveness in pediatric CF patients during treatment for PEx. One strength of this study is the relatively large number of patients tested. One of the study's limitation is the retrospective analysis. Also, while patients in this study underwent spirometry testing to evaluate lung function after 1 week of therapy, a clear indication to justify BD response testing was not documented. While we did not find any proof that this selection was not random, we cannot exclude a selection bias could affect the results of this study.

Conclusion:

Significant BD response in hospitalized children treated for a CF pulmonary exacerbation is rare, is not related to age, severity of lung disease or potential recovery of lung function, and does not lead to immediate changes in clinical management in the majority of patients. BD response is poorly related to baseline, and recovery of FEV_1. These data suggest that routine testing of bronchodilator response during CF PEx is not indicated, and should be limited to selected patients when clinically needed.

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