Bronchodilator responsiveness in children with primary ciliary dyskinesia

Elias Seidl [1,2], Dvir Gatt [1], Wallace B. Wee [1], David Wilson[1], Felix Ratjen [1,3] and Hartmut Grasemann [1,3,4]

[1]Division of Respiratory Medicine, Department of Pediatrics, The Hospital for Sick Children, Toronto, ON, Canada. [2]Division of Respiratory Medicine, University Children's Hospital Zurich, Zurich, Switzerland. [3]Translational Medicine Program, Research Institute, Hospital for Sick Children, Toronto, ON, Canada. [4]University of Toronto, Toronto, ON, Canada.

Corresponding author: Hartmut Grasemann (Hartmut.Grasemann@sickkids.ca)

Shareable abstract (@ERSpublications)
Children with PCD and a positive bronchodilator response are at risk of accelerated lung disease progression and may require additional treatment; adding bronchodilator response testing to routine spirometry can have a clinical benefit https://bit.ly/3QRymWK

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Abstract

Background Reversible airway obstruction is common in children with primary ciliary dyskinesia. However, the diagnostic value of adding bronchodilator (BD) response testing to routine spirometry is unclear.

Methods This is a retrospective analysis of pulmonary function test results obtained from children with primary ciliary dyskinesia seen as outpatients at the Hospital for Sick Children, Toronto. Spirometry results were collected for every appointment with BD response testing ("Visit", with pre-BD and post-BD measurements) as well as for the previous ("Baseline") and following ("Follow-up") encounters.

Results A positive BD response was seen in 86 out of 474 (18.1%) of the pulmonary function tests from 82 children with primary ciliary dyskinesia. BD responsiveness was associated with a significant absolute change (±SD) in % predicted forced expiratory volume in 1 s (FEV_1) from Baseline to Visit pre-BD (−6.5±10.3%, p<0.001), but not from Baseline to Follow-up (0.4±10.8, p=0.757). Antimicrobial therapy was initiated more commonly following a Visit with a positive BD response (OR 3.8, 95% CI 2.2–6.6) compared to no BD response. Children with a positive BD response had a greater annual decline in FEV_1 % predicted compared to those with no BD response (−0.9% per year *versus* −0.5% per year, p<0.001). The annual decline in FEV_1 % predicted was greater in children with multiple compared to one measured positive BD responses (−1.3% per year *versus* −0.6% per year, p<0.001) and in those not treated with antibiotic therapy following a positive BD response compared to those treated with antibiotics (−1.1% *versus* −0.6%, p<0.001).

Conclusion A positive BD response in children with primary ciliary dyskinesia may help identify those at risk for accelerated lung disease progression.

Introduction

Primary ciliary dyskinesia (PCD) is a rare, mainly autosomal recessive inherited, multi-organ disease that is characterised by dysfunctional motile cilia. In the respiratory tract, PCD causes impaired mucociliary clearance, neonatal respiratory distress, chronic nasal congestion, sinusitis and chronic wet cough [1–3]. Recurrent airway infections and inflammation are common, leading to bronchiectasis and irreversible lung damage [2, 4]. The diagnosis of PCD can be challenging and involves typical clinical features, measurement of nasal nitric oxide, structural and functional analysis of cilia and genetic testing [5]. PCD has an estimated incidence of 1 per 10 000–20 000 [6–8]. The prevalence of PCD is difficult to determine, largely due to inadequacies of diagnostic methods [9].

Owing to the paucity of high-quality studies, clinical care practice for people with PCD is mainly adopted from other diseases including cystic fibrosis (CF). Current guidelines for people with PCD recommend at

least biannual clinic visits with pulmonary function testing (PFT) to monitor lung disease [5]. In children with PCD, reversible airway obstruction has been reported and inhaled β2-agonists are frequently prescribed [10, 11]. However, the diagnostic value as well as clinical consequence of a positive bronchodilator (BD) response in children with PCD remains unclear [12].

The aim of this study was to determine the frequency of reversible airway obstruction in children with PCD, and whether a positive BD response at routine clinical testing helps predict clinical outcomes.

Methods

PFT results from children with PCD at the Hospital for Sick Children (SickKids), Toronto, between 2009 and 2021 were analysed. The study was approved by the local Research Ethics Board (#1000078911). PCD was diagnosed according to American Thoracic Society (ATS) guidelines [5]. All PCD patients performing PFTs as part of routine care were eligible for this retrospective single-centre study. Participants were identified by searching the SickKids Respiratory Medicine PFT database. Spirometry results (forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC)) were calculated using published Global Lung Function Initiative equations [13] and expressed as % predicted. A positive BD response was defined as >12% in predicted and >200 mL change in absolute FEV_1 or FVC following inhalation of albuterol using a spacer, as per ATS guidelines [14]. Airway microbiology testing was performed in expectorated sputum or throat swabs as per clinical routine. Demographics and clinical characteristics were abstracted from electronic medical records by chart review. This study consisted of two parts.

For the first part, we collected spirometry results for all encounters with BD response testing ("Visit") and the previous ("Baseline") as well as the following ("Follow-up") encounters and created two groups: group 1 had positive BD responsiveness at Visit and group 2 had no BD responsiveness at Visit. We analysed the change in FEV_1 % predicted from Baseline to Visit as well as from Visit to Follow-up for each group and compared the results.

Second, we compared the annual FEV_1 % predicted decline in PCD children with at least one positive BD response to those with only negative BD responses during the study period.

Statistical analysis was performed using SPSS software v27.0 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism v8.4.3 (GraphPad Software, San Diego, CA, USA). All continuous variables were tested for normal distribution (Shapiro–Wilk test) and data are presented as n (%), mean±SD, mean (95% CI) or median (interquartile range (IQR)). Categorical variables were compared using chi-square test. Differences between groups were analysed using two-sample unpaired t-test or Mann–Whitney U test, where appropriate. Paired t-test was used to compare related samples. Odds ratio (95% CI) was calculated to quantify the association between BD responsiveness and initiation of antimicrobial treatment. To calculate annual pre-BD FEV_1 % predicted decline, linear regression models were used and tested for significance by ANOVA. To test the relationship between the slopes, a hypothesis test on the difference between regression coefficients was performed. All models were adjusted for the number of visits with PFTs. A p-value <0.05 was considered significant.

Results

During the study period, 99 children with PCD had performed spirometry testing. Of these, 17 children were excluded because they never underwent BD testing. Of the remaining 82 children, a total of 474 PFTs with BD response testing were performed and used for the analysis. Genetic testing was performed in 76 patients; bi-allelic pathogenic variants included *DNAH5* (n=22), *DNAH11* (n=7), *CCDC39* (n=7), *LRRC6* (n=4), *CCNO* (n=2), *CCDC40* (n=2), *DRC1* (n=2), *SPAG1* (n=2), *DNAAF2/KTU* (n=1), *DNAAF3*, (n=1), *DNAAF4* (n=1), *DNAH9* (n=1), *DNAI1* (n=1), *DNAI2* (n=1), *HYDIN* (n=1) and *ZMYND10* (n=1). For six patients, genetic testing revealed no pathogenic variants known to cause PCD. Based on the genotype, PCD children were divided into two groups: "mild" (*DNAH5*, *DNAH11*, *DNAAF3*, *LRRC6*, *ZMYND10*, *DNAH9*, *DNAI1*, *DNAAF2/KTU*, *DNAAF4* and *DNAI2*) and "severe" (*DRC1*, *HYDIN*, *CCDC39*, *CCNO*, *SPAG1* and *CCDC40*) [15, 16]. None of the patients included in this study had a physician diagnosis of asthma or allergic rhino-conjunctivitis. Laboratory test results revealed normal blood total IgE levels (median 25.0 $kU \cdot L^{-1}$, IQR 15.2–77.0 $kU \cdot L^{-1}$). Clinical and demographic details for the study cohort are listed in table 1. The median (IQR) number of PFTs with BD response testing per patient was 4.00 (IQR 2.00–7.25). Airway microbiology culture results at Visit were positive in 305 out of 474 (64.3%); the most common were *Haemophilus influenzae* (36%), *Staphylococcus aureus* (22%), *Streptococcus pneumoniae* (12%) and *Pseudomonas aeruginosa* (9%).

TABLE 1 Characteristics of study cohort

Number of patients (%)	82 (100)
Female sex	37 (45.1)
Race	
White	50 (61)
Asian	9 (11.0)
Black	3 (3.7)
Mixed	14 (17.1)
Data not available	6 (7.3)
Age at diagnosis in years	8.0±5.2
EM defects	
ODA defect	16 (19.5)
Combined ODA and IDA defect	21 (25.6)
Central pair defect	13 (15.9)
No ultrastructural defect	8 (9.8)
EM not done or data not available	24 (29.2)
Situs in versus	34 (41.5)
Diagnostic nNO[#]	63 (76.8)
Gestational age in weeks	
<32	– (0)
32–37	23 (28.0)
>37	59 (72.0)

Data are presented as n (%) or mean±SD. EM: electron microscopy; ODA: outer dynein arm defect; IDA: inner dynein arm defect; nNO: nasal nitric oxide. [#]: diagnostic nNO was defined as a test result <77 nL·min^{-1}.

The mean±SD absolute change in FEV_1 from pre- to post-BD testing was 140.1±136.3 mL and the mean change in FEV_1 % predicted from pre- to post-BD was 5.0±5.5% (figure 1). Inhaled corticosteroid (ICS) therapy was given to 50 out of 82 individuals, at 293 out of 472 encounters (62.1%). The mean change in FEV_1 % predicted from pre- to post-BD was not different whether receiving (n=294 out of 474 encounters) or not receiving ICS (5.0±4.9% *versus* 5.1±6.2%, p=0.853). A total of 86 out of 474 tests (18.1%) revealed a positive BD response according to European Respiratory Society/ATS criteria [14]; when a 12% improvement in FEV_1 % predicted was used as the only criterion, 101 out of 474 tests (21.3%) were positive. For 34 out of 82 tested patients (41%) there was at least one recorded positive BD response. BD responsiveness was not associated with sex (p=0.059), ethnicity (p=0.167), airway microbiology culture positivity (p=0.933) or age at diagnosis (p=0.074). BD responsiveness was more common at a younger age (table 2). Data from 428 out of 474 encounters documenting clinical symptoms

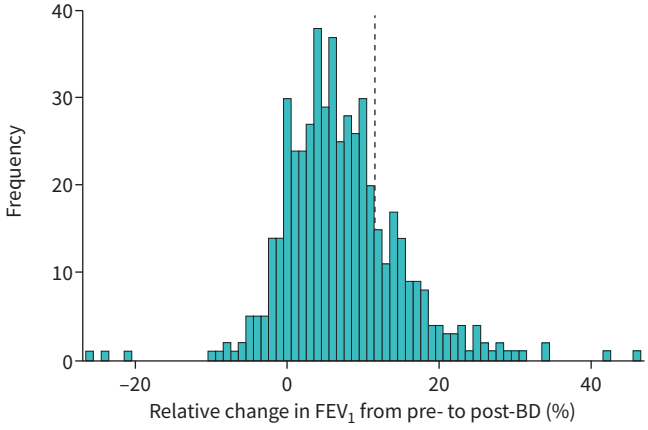

FIGURE 1 The relative change in forced expiratory volume in 1 s (FEV_1) % predicted post-bronchodilator (BD) inhalation presented as frequencies of tests (n=474). The dashed line indicates a 12% change in FEV_1 % predicted.

TABLE 2 Spirometry results of the study cohort

	Total cohort	Positive BD response	No BD response	p-value[#]
Number of patients (%)	474 (100)	34 (41)	48 (59)	
PFTs with BD response testing	474 (100)	86 (18.1)	388 (81.9)	–
Age at PFT in years	12.8±3.4	11.8±3.0	13.0±3.4	**<0.001**
FEV_1 % predicted				
Baseline	76.5±16.5	76.8±16.6	76.5±16.5	0.883
Visit, pre-BD	75.5±16.8	70.2±15.2	76.7±16.8	**0.001**
Follow-up	76.7±16.6	77.2±15.6	76.6±16.8	0.782
Δ Baseline to Visit, pre-BD	−1.0±10.5	−6.5±10.3	0.2±10.2	**<0.001**
Δ Baseline to Visit, post-BD	4.1±10.8	6.2±10.7	3.6±10.8	**<0.001**
Δ Baseline to Follow-up	0.0±10.9	0.4±10.8	−0.1±10.9	0.724
Time between Baseline and Visit (months)	4.7±3.6	4.6±3.3	4.8±3.7	0.717
Time between Visit and Follow-up (months)	4.9±4.8	4.3±4.0	5.0±5.0	0.232
Antimicrobial treatment initiated after Visit	114/474 (24.1)	40/86 (46.5)	74/388 (19.1)	**<0.001**

Data are presented as n (%) or mean±SD. Categorical variables were compared using chi-square test. All continuous variables were tested for normal distribution (Shapiro–Wilk test) and differences between groups analysed using two-sample unpaired t-test or Mann–Whitney U test, as appropriate. Bold values indicate significant differences. BD: bronchodilator; PFT: pulmonary function test; FEV_1: forced expiratory volume in 1 s. [#]: comparison between children with positive or no BD response.

were available for review. Worsened respiratory symptoms (*e.g.* cough) were documented for 121 (28.3%) of the visits, and these were not associated with a positive BD response (p=0.471).

BD responsiveness was associated with a significant absolute change in FEV_1 % predicted from Baseline to Visit pre-BD (−6.5±10.3%, p<0.001) and from Baseline to Visit (6.2±10.7%, p<0.001), and was more common in individuals with a >10% drop in FEV_1 % predicted from Baseline to Visit than in those with <10% change (37.6% (32 out of 85) *versus* 13.8% (52 out of 376); p<0.001). Individuals with no BD responsiveness had no change in FEV_1 % predicted from Baseline to Visit pre-BD (−0.2±10.2%, p=0.724). The change in FEV_1 % predicted was similar between Baseline and Follow-up regardless of BD responsiveness at Visit (0.4±10.8%, p=0.757 *versus* −0.1±10.9%, p=0.862) (figure 2). Antimicrobial

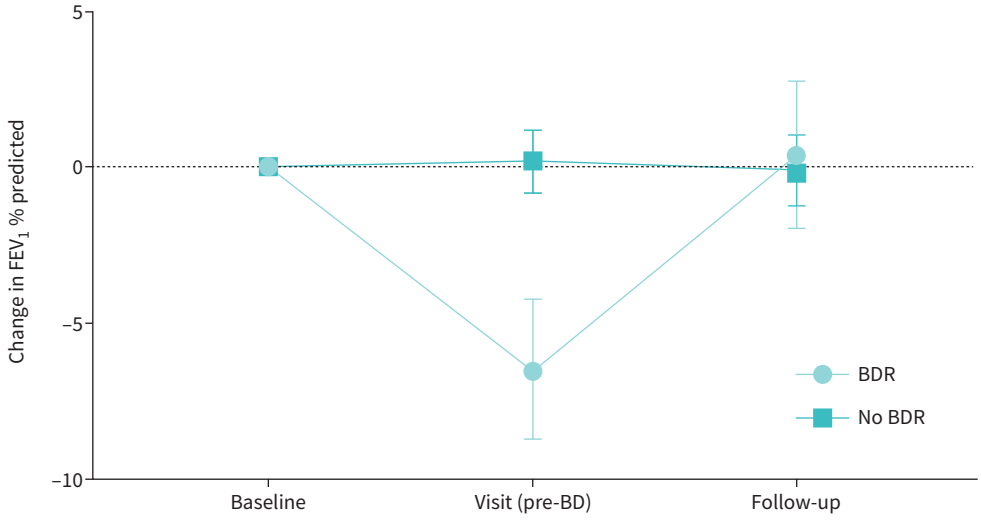

FIGURE 2 Absolute change from Baseline to Visit (pre-bronchodilator (BD)) and Follow-up in forced expiratory volume in 1 s (FEV_1) % predicted. Data are presented as means with 95% confidence intervals. The dashed line indicates baseline. BDR: bronchodilator response.

therapy was initiated more frequently following a Visit with a positive BD response than with no BD response (OR 3.8, 95% CI 2.2–6.6). However, at Follow-up, change in FEV_1 % predicted did not differ whether treated or not treated with antimicrobials for both individuals with BD response (2.6±11.0% *versus* −0.5±11.0%, p=0.486) or without (0.2±9.5% *versus* −0.8±11.4%, p=0.442) (table 2).

Longitudinal analysis of PFT data from all 82 children with PCD during the 12-year observation period revealed an average annual decline in pre-BD FEV_1 % predicted of −0.6% per year (95% CI −0.7– −0.4%, p<0.001). Children with one or more positive BD response test (n=34) had a greater annual decline in pre-BD FEV_1 % predicted compared to those with no BD response (n=48) (−0.9%, 95% CI −1.2– −0.7%, *versus* −0.47%, 95% CI −0.3– −0.6%; p<0.001). To test for prematurity as a potential risk factor for lung disease progression, preterm birth was added to the regression models as a confounder, and had no effect on the annual PFT decline. The annual decline was more pronounced in children with two or more documented positive BD responses (n=15) compared to one positive BD response (n=19) (−1.3% per year, 95% CI −1.0– −1.7% per year, *versus* −0.6% per year, 95% CI −0.4– −0.7% per year; p<0.001). Further, those not treated with antibiotic therapy following a Visit with a positive BD response had a greater pre-BD FEV_1 % predicted decline compared to those receiving antibiotic therapy (−1.1%, 95% CI −1.6– −0.7%, *versus* −0.6%, 95% CI −1.1– −0.2%; p<0.001) (table 3). The annual FEV_1 % predicted decline did not differ between mild and severe PCD genotypes across children with positive BD responsiveness (p=0.123)

Discussion

In this analysis we found that reversible airway obstruction demonstrated on routine PFTs was common in a large, well-characterised paediatric PCD cohort. BD responsiveness was associated with a temporary decline in (pre-BD) FEV_1 % predicted compared to previous Baseline, and children with a positive BD response were more likely prescribed antimicrobial therapies. Longitudinal analysis of PFT data revealed an annual decline in FEV_1 % predicted of −0.6% per year for the entire cohort but children with reversible airway obstruction on multiple occasions as well as those not receiving antibiotic therapy following a positive BD test had a significantly greater annual decline in FEV_1 % predicted (−1.3% per year and −1.1% per year, respectively).

Our observation of a positive BD response in 18% of patients matches an earlier report by Keenan *et al.* [11], who found a positive BD response in 17% of 47 children with PCD. In another retrospective study, Levine *et al.* [10] reported results from BD response testing in 46 children with PCD. Reversible airway obstruction, defined as ⩾10% decline in FEV_1 % predicted, was present in 26 children (56.5%). Of note, although the history of recurrent wheezing was present in almost half of these patients, reversible airway obstruction was not associated with markers of allergic asthma such as a positive family history, increased blood eosinophil counts, elevated serum IgE or atopy. Smaller patient numbers, a lower threshold for definition of significance in BD response and a preselection towards children with recurrent wheeze likely contributed to the greater prevalence of BD responsiveness in their studies compared to ours.

ICS are commonly prescribed in PCD often without evidence of type 2 airway inflammation [17]; in our cohort ICS therapy was prescribed in 62.1% of the analysed encounters. While current guidelines recommend ICS therapy in PCD patients with co-existing asthma or wheezing [18, 19], in our cohort no

TABLE 3 Annual decline in FEV_1 according to BD response positivity, antimicrobial treatment initiated after Visit and number of positive BD responses

	Annual change in FEV_1 % predicted (95% CI)	p-value
No BD responsiveness	−0.5 (−0.3– −0.6)	**<0.001**
No antimicrobial treatment	−0.3 (−0.5– −0.1)	**<0.001**
Antimicrobial treatment	−0.7 (−1.0– −0.3)	**0.001**
BD responsiveness	−0.9 (−1.2– −0.7)	**<0.001**
No antimicrobial treatment	−1.1 (−1.6– −0.7)	**<0.001**
Antimicrobial treatment	−0.6 (−1.1– −0.2)	**0.009**
One positive BD response test	−0.6 (−0.4– −0.7)	**<0.001**
⩾2 positive BD response tests	−1.3 (−1.0– −1.7)	**<0.001**

To calculate annual decline in FEV_1 % predicted, pre-BD, linear regression models were used and tested for significance by ANOVA. The models were adjusted for the number of visits per participant. Bold values indicate significant differences. FEV_1: forced expiratory volume in 1 s; BD: bronchodilator.

participant had a documented diagnosis of asthma. The rational for prescribing long-term ICS therapy in our cohort remains unclear and was not the focus of this study. It can be speculated that ICS therapy in individual patients was initiated in response to recurrent wheezing episodes following viral respiratory infections.

Our data suggest that BD responsiveness in children with PCD is associated with a temporary decline in lung function that can recover with or without antimicrobial therapy, given that the FEV_1 % predicted at next follow-up after 4–5 months was similar to recorded baselines prior to the positive BD response, regardless of antibiotic therapy. It is therefore conceivable that the observed decline in lung function was not always caused by bacterial infections requiring antibiotic therapy. Other explanations could be noninfectious exacerbations or viral infections. If the latter, this may help explain the observed association of BD responsiveness with younger age, because viral infections are more common in younger than in older children [20]. An association of respiratory tract infections with reversible airway obstruction is well documented for adults without an underlying chronic respiratory condition [21].

However, the analysis of longitudinal PFT data revealed that a positive BD response not treated with antibiotics was in fact associated with a greater loss in pulmonary function over time. Previous cross-sectional and longitudinal analyses of PFT data in PCD reported a high degree of variation in the progression of lung disease. Some authors reported stable lung function once the PCD diagnosis was established and treatments were initiated, whereas others described lung disease progression with increasing age [4, 22–25]. Ellerman and Bisgaard [26] analysed longitudinal PFT data from 24 PCD patients diagnosed at different ages and concluded that aggressive treatment could prevent further lung damage. Other factors potentially contributing to variability in clinical presentation and lung disease progression include differences in the disease-causing PCD genetics and their consequences for the structure or function of the respiratory cilia [16].

In children with PCD and BD responsiveness, further studies are needed to assess the benefit of intensified treatment, including chest physical therapy as well as antimicrobial or anti-inflammatory agents. Of note, while the annual decline in FEV_1 % predicted in those with positive BD response was significantly greater if not treated with antibiotics in our study, there appeared to be no difference in annual PFT decline in children with PCD who were treated with antibiotics compared to those with positive or negative BD response prior to initiation of treatment. We therefore speculate that antibiotic therapy, maybe in combination with optimised airway clearance, does result in measurable long-term benefits that are not detectable in short-term follow-up.

In a recent analysis of PFT data in a cohort of children with CF, we showed that a significant BD response in CF pulmonary exacerbation (PEx) is rare and not related to the severity of lung disease or potential recovery of lung function, and does not lead to changes in clinical management [27], demonstrating that routine BD response testing in CF PEx is not clinically meaningful. This is in contrast to our findings in children with PCD, in whom BD responsiveness is common and a relevant correlation with clinical outcomes seems to exist. However, the observation that a positive BD response in PCD was also linked to the magnitude of decline in pre-BD FEV_1 % predicted from the previous baseline may suggest that even though a positive BD response is associated with poorer outcome, a significant drop in FEV_1 % predicted alone could be indicative of a PCD PEx requiring initiation of therapy.

There are several limitations to this retrospective single-centre study. First, standard care of children with PCD does not include routine BD response testing and the rationales for ordering PFTs with BD response testing may vary between physicians and centres. Also, children with more severe pulmonary involvement might be seen more often in clinic and therefore be overrepresented in this study. To overcome this issue, we adjusted the statistical model for the individual number of visits. However, children with PCD in the absence of clinical symptoms not performing PFT might have been excluded from this analysis completely, even though PFTs are usually performed at every visit. In addition, patient- or parent-reported symptoms were not included in this analysis, and we cannot comment on the association between respiratory symptoms and PFT findings. Finally, although BD response seemed to be associated with PCD PEx, the mechanisms resulting in reversible airway obstruction remain unclear and contributing factors might have been missed.

In conclusion, our data show that reversible airway obstruction is common in children with PCD and is reflective of a temporary decline in FEV_1 % predicted. BD responsiveness may help to identify children with PCD at risk for lung disease progression. Further studies are needed to assess the benefit of different treatment options.

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Ethics statement: The study was approved by the local Research Ethics Board (REB #1000078911).

Conflict of Interest: There are no competing interests for any author.

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