ORIGINAL ARTICLE

Bronchodilator responsiveness assessed by forced oscillometry and multiple breath washout techniques in preschool children

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ABSTRACT

Importance: The forced oscillation (FOT) and multiple breath washout (MBW) techniques are passive tests of lung function, and are reliable for preschool-age children. There has not been comparison testing to determine which test could more accurately differentiate between healthy controls and poorly controlled asthmatics, or differentiate a response to bronchodilator administration.

Objective: To determine whether the MBW and/or FOT could differentiate between healthy controls and poorly controlled asthmatics, and whether the two tests could detect a response to bronchodilator administration.

Methods: Twenty-eight healthy controls and 23 poorly controlled asthmatics 3–6 years of age participated. All subjects were administered the MBW followed by the FOT. A bronchodilator was then administered and testing was repeated. Wilcoxon Rank Sum tests were used to compare the difference between healthy controls and poorly controlled asthmatics. Wilcoxon Signed Rank tests were used to compare the pre- and post-bronchodilator values.

Results: Neither MBW nor FOT differentiated healthy controls from poorly controlled asthmatics (pre-bronchodilator data); both groups had similar baseline gas mixing and airway mechanics. There was no improvement in any MBW outcomes post-bronchodilator administration. FOT detected a significant and similar degree of improvement in the airway mechanics in both groups.

Interpretation: Neither MBW nor FOT differentiated between poorly controlled asthmatics (when well) and healthy controls. MBW did not detect a significant bronchodilator response in either subject group, whereas FOT detected a similar degree of bronchodilator responsiveness in both groups. This discrepancy may reflect differential changes in airway mechanics and gas mixing properties in response to bronchodilators.

KEYWORDS
Forced oscillation technique, Multiple breath washout, Pediatric lung function measurement, Pediatric asthma

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INTRODUCTION

Asthma is one of the most common chronic childhood diseases, affecting 4.7% of children 0–4 years of age and 9.8% of children 5–14 years of age in the United States.[1] Measuring lung function in preschool-age children is difficult. Traditional methods of measuring lung function that are typically used in older children and adults (spirometry and plethysmography) often yield uninterpretable results when performed on young children due to their inability to cooperate fully or perform proper testing techniques.[2, 3] In 2007, the American Thoracic Society (ATS) and European Respiratory Society (ERS) published a policy statement regarding the application and interpretation of pulmonary function tests (PFTs) in preschool-age children.[2] The ATS/ERS policy statement stated that two passive tests of lung function, the multiple breath washout (MBW) and the forced oscillation technique (FOT), were feasible and well tolerated in preschool-age children.[2]

In this study we compared MBW and FOT in preschool-age children, to determine, 1) whether the MBW and FOT could differentiate between healthy controls and subjects with poorly controlled asthma who were not currently experiencing an asthma exacerbation, and 2) whether the two tests could detect response to bronchodilator administration. Asthma is an obstructive lung disease characterized by remissions and exacerbations. When a patient's asthma is well controlled, minimal impact on their baseline lung function should occur. However, if the patient's asthma is poorly controlled, it is more likely to affect their daily lung function. Therefore, we reasoned that by testing children with poorly controlled asthma, possible persistent abnormalities of gas mixing and lung mechanics would increase the likelihood of detecting differences between asthmatics and controls. We hypothesized that both the MBW (a measurement of gas mixing) and the FOT (a measurement of airway mechanics) would differentiate healthy controls from poorly controlled asthmatics both by their baseline characteristics, as well as their degree of bronchodilator response. We further hypothesized that FOT, as a test of mechanics, would be a better reflection of bronchodilator responsiveness than MBW, a test of gas mixing. Our results suggest that healthy controls and well asthmatics (despite their poor control) likely have similar characteristics of gas mixing, and similar airway mechanics. In addition, we report that FOT is a better test of bronchodilator responsiveness than MBW.

METHODS

The study was conducted in the Division of Pulmonary Medicine at The Children's Hospital of Philadelphia, and approved by the institutional review board. We studied 28 healthy controls and 23 poorly controlled asthmatics, who were children with recurrent wheeze between 3 and 6 years of age, recruited from local general pediatric practices. All subjects' parent(s) provided written informed consent. Demographic information appears in Table 1. All subjects' asthma status (control vs. asthmatic) was verified using the International Study of Asthma and Allergies in Children (ISAAC) questionnaire.[4,5] Exclusion criteria for all subjects included other co-morbid cardiopulmonary diseases, history of prematurity, and the presence of a respiratory illness at the time of testing. Healthy controls were excluded if they had any history of asthma, wheeze, or respiratory diseases. Asthmatics were excluded if currently experiencing an asthma flare (parental perception and/or abnormal physical examination), use of systemic corticosteroids in the previous 48 hours, or use of bronchodilators within 4 hours of beginning the study. The Childhood Asthma Control Tool (C-ACT) was administered to all asthmatics to assess their asthma control in the previous 28 days.[6,7] Only poorly controlled asthmatics, as identified by a C-ACT score of ≤ 19 were enrolled in the study.

First the Multiple Breath Washout (ECO MEDICS AG EXHALYZER® - Switzerland) test was administered. Subjects breathed room air through a facemask securely held to their face by the study examiners, until a regular respiratory pattern was observed. After at least 5 stable tidal breaths, 100% oxygen was administered, and subjects breathed until their exhaled nitrogen concentration reached<2% for 5 consecutive breaths. The facemask was then removed, and subjects breathed normally to re-equilibrate with room air. The MBW tests were repeated until the functional residual capacity (FRC) and lung clearance index (LCI) on two tests agreed within 10%. Outcomes measured were FRC and the LCI at two degrees of N_2 washout (5%, 2.5%).

Forced Oscillation Technique (COSMED® Quark i2m – Italy) testing was then completed. Subjects sat comfortably, and breathed through a mouthpiece. Subjects' noses were pinched shut and cheeks were supported (by the study staff) to ensure that there was neither air leak, nor measurement of cheek shunt oscillations. A pseudo-random oscillation pattern containing 4–48 Hz was then administered. The oscillations were generated over a period of 8 seconds, and subjects were instructed to breathe comfortably and tidally during the oscillation period. Subjects were given 30–60 second rests between trials. Testing continued until each subject completed 4–5 FOT administrations with at least 95% coherence on at least 21 of 23 administered frequencies of 4–48 Hz. Outcomes measured were the resonance frequency (f_0), resistance at 10 Hz and resistance at the resonance frequency (R10 and Rf_0, respectively), the difference in resistance between 6 Hz and 20 Hz (R6-R20), reactance at 6 Hz (X6), reactance at 10 Hz (X10), and the low frequency reactance area (AX).

Subjects were then administered 2 puffs of albuterol (Ventolin®; GlaxoSmithKline, Research Triangle Park, NC, USA) via spacer (OptiChamber; Respironics New Jersey, Inc. Parsippany, NJ, USA). After 10 minutes elapsed, both the MBW and FOT were repeated. All except two subjects, one asthmatic and one healthy control who became anxious, were able to complete the testing and included in the data analysis.

Study data were managed using a secure REDCap electronic database hosted at The Children's Hospital of Philadelphia.[8] Data analysis was performed using SAS (edition 9.3; 2012, Cary, NC, USA). The data was found to be non-parametric, therefore, the Wilcoxon Rank Sum tests were used to compare the differences between healthy controls and asthmatics. Wilcoxon Signed Rank tests were used to compare the pre- and post-bronchodilator values. Since several different comparisons were conducted, Bonferroni corrections were used to control the overall type 1 error rate. Initial power calculations generated a desired sample size of 30 asthmatics and 30 healthy controls. Sample size analysis for the 28 healthy controls and 23 asthmatics estimated 80% power to detect an effect size between asthmatics and controls of 0.94 SD using MBW and 1.0 using FOT, and 80% power to detect an effect size between pre-and post-bronchodilator results of 0.72 using MBW and 0.77 using FOT in asthmatics; and an effect size of 0.65 using MBW and 0.69 using FOT in controls.

RESULTS

Demographic characteristics (Table 1)

The ages, heights, and BMIs were similar in both asthmatics and healthy controls. We had relatively equal proportions of males and females. The majority of our subjects were African American and lived in an urban environment, characteristic of the surrounding community and recruitment area. All asthmatics had previous emergency department visits for asthma, and the majority had been hospitalized, and/or received oral corticosteroid courses in the past 12 months.

Baseline testing (Table 2)

There were no significant differences in the baseline lung clearance index (LCI) or functional residual capacity (FRC) between the two groups (Table 2a). In addition, no

TABLE 1 Demographic Information

	Overall (N=51)	Asthma (N=23)	Healthy Control (N=28)
Age (y) $\overline{X}$(SD)	5.2 (1.1)	5.0 (1.0)	5.2 (1.1)
Height (cm) $\overline{X}$(SD)	112.2 (8.7)	112.4 (9.4)	112.1 (8.3)
BMI $\overline{X}$(SD)	16.5 (2.1)	16.6 (2.6)	16.4 (1.6)
Total C-ACT Score $\overline{X}$(SD)	16.0 (3.4)	16.0 (3.4)	-
Gender N(%)			
Female	31 (61)	12 (52)	19 (68)
Male	20 (39)	11 (48)	9 (32)
Race N(%)			
Black	35 (69)	15 (65)	20 (71)
White	11 (22)	5 (22)	6 (21)
More than One Race	5 (10)	3 (13)	2 (7)
Ethnicity N(%)			
Hispanic or Latino	4 (8)	4 (18)	0
Not Hispanic or Latino	46 (90)	18 (68)	28 (100)
Unknown/ Not Reported	1 (2)	1 (4)	0
Environment N(%)			
Rural	1 (2)	1 (4)	0
Suburban	8 (16)	4 (17)	4 (14)
Urban	40 (78)	16 (70)	24 (86)
Unknown/ Not Reported	2 (4)	2 (9)	0
Asthma Exacerbations $\overline{X}$(SD)			
Emergency Department Visits		4.9 (6.0)	
Inpatient Hospitalizations		3.0 (6.4)	
Oral Corticosteroids in Past 12 Months		3.5 (6.1)	

C-ACT, Childhood Asthma Control Tool.

significant differences were found between the outcome variables measured by FOT (Table 2b). Thus, neither MBW nor FOT were able to differentiate between healthy controls and poorly controlled asthmatics based on their baseline (pre-bronchodilator) data.

TABLE 2 Baseline data for MBW and FOT

2a) MBW

Value	Group	Pre-bronchodilator	*P*
LCI 2.5%	Healthy Controls	7.63 (7.29,8.25)	0.40
	Asthmatics	7.85 (7.42, 8.59)	
LCI 5.0%	Healthy Controls	5.54 (5.19, 5.91)	0.96
	Asthmatics	5.53 (5.36, 5.89)	
FRC (L)	Healthy Controls	0.85 (0.63, 1.01)	0.50
	Asthmatics	0.78 (0.65, 0.95)	

LCI, lung clearance index ; FRC, functional residual capacity.

2b) FOT

Value	Group	Pre-bronchodilator	*P*
R10 (hPa/L/sec)	Healthy Controls	7.95 (7.00, 8.84)	0.96
	Asthmatics	7.83 (6.76, 9.32)	
R6-R20 (hPa/L/sec)	Healthy Controls	1.74 (0.97, 2.58)	0.11
	Asthmatics	2.42 (1.75, 3.39)	
X6 (hPa/L/sec)	Healthy Controls	-3.64 (-4.92, -2.91)	0.86
	Asthmatics	-3.84 (-5.30, -2.77)	
X10 (hPa/L/sec)	Healthy Controls	-2.95 (-3.62, -2.00)	0.31
	Asthmatics	-3.15 (-4.02, -2.39)	
f_0 (Hz)	Healthy Controls	25.21 (21.42, 28.90)	0.99
	Asthmatics	25.57 (22.23, 29.97)	
Rf_0 (hPa/L/sec)	Healthy Controls	6.73 (5.39, 7.60)	0.37
	Asthmatics	6.26 (5.46, 7.06)	
AX (cmH_2O/L)	Healthy Controls	37.07 (27.69, 54.54)	0.61
	Asthmatics	42.75 (28.36, 59.27)	

Post-bronchodilator testing (Table 3)

There were no improvements in any of the MBW outcomes post-bronchodilator administration (Table 3a) for either healthy controls or asthmatics. In contrast, both healthy controls and asthmatics had similar, significant, degrees of improvement in their airway mechanics as measured by the FOT outcome variables post-bronchodilator administration (Table 3b). The only parameter showing a tendency to more responsiveness to bronchodilator in the asthmatics compared to controls was the R6-R20 ($P = 0.058$).

DISCUSSION

Our study was the first direct comparison of MBW and FOT used to assess lung function in preschool-age children. Additionally, our study was the first to use the C-ACT to assess asthma control and selectively compare poorly controlled asthmatics with healthy controls using MBW and FOT in order to maximize the opportunity for the tests to show group differences if they existed. Neither MBW nor FOT was able to differentiate between healthy controls and asthmatics baseline data and/or degree of bronchodilator response despite a history of poor control in the asthma subjects. MBW was unable to detect a bronchodilator response in either group of subjects. In contrast, FOT detected a significant and similar, magnitude of bronchodilator response in all subjects. These data suggest that changes in airway mechanics after bronchodilator administration predominate over changes in gas mixing.

It is difficult to confirm asthma in preschool children less than the age of 6 who have recurrent wheeze. We used the ISAAC questionnaire as the best approximation of defining the symptoms of the recurrently wheezing preschooler. This is an approach that has been taken previously.[4,5] It is fair to question whether these children had asthma in the strict sense, but they all clearly had recurrent wheeze. In addition, we evaluated the degree of asthma control in the asthmatics by using the Childhood Asthma Control Test (C-ACT), which has been validated down to the age of 4 years.[6,7]

Several previous studies have assessed the ability of MBW and FOT to compare healthy controls and children with obstructive lung diseases (cystic fibrosis and asthma), but none have compared the two techniques directly.[9-11] Previous studies comparing MBW in young children with asthma versus healthy controls suggest that children with asthma have greater ventilation inhomogeneity than healthy controls before, but not after, bronchodilator administration.[9,10]

Gustaffson[9] and Zwittersloot et al[10] found that healthy controls and asthmatics (of varying degrees of control) had different baseline LCI. Similar to our findings, Zwittersloot et al[10] found that neither healthy controls nor asthmatics had a significant decrease in LCI post-bronchodilator administration. Gustaffson[9] found a significant decrease in LCI post-bronchodilator administration in asthmatics; healthy controls were not assessed post-bronchodilator administration.

Previous studies conducted with FOT have also had variable results.[12-20] Similar to our results, Thamrin[13,14], Hellinckx[15], and Robinson[16] found no baseline differences in the airway mechanics of healthy controls and asthmatics as measured by FOT. Oostveen et al[17] found a significant baseline difference in various resistances, reactances and

TABLE 3 Response to bronchodilator administration

3a) MBW

Value	Group	Pre-bronchodilator	Post-bronchodilator	Difference Pre and Post¶,*	*P* ¶
LCI 2.5%	Healthy Controls	7.63 (7.29,8.25)	7.96 (7.41, 8.47)	0.1 (-0.07, 0.76)	0.05
	Asthmatics	7.85 (7.42, 8.59)	8.11 (7.52, 8.80)	0.3 (-0.27, 0.57)	0.14
LCI5.0%	Healthy Controls	5.54 (5.19, 5.91)	5.69 (5.38, 5.94)	0.19 (-0.07, 0.39)	0.05
	Asthmatics	5.53 (5.36, 5.89)	5.44 (5.20, 5.83)	-0.01 (-0.32, 0.35)	1.00
FRC (L)	Healthy Controls	0.85 (0.63, 1.01)	0.87 (0.61, 1.01)	0.02 (-0.06, 0.04)	0.66
	Asthmatics	0.78 (0.65, 0.95)	0.89 (0.66, 1.03)	0.04 (-0.03, 0.17)	0.14

LCI, lung clearance index; FRC, functional residual capacity.

¶ There was no significant change in MBW parameters after bronchodilator administration for either Healthy Controls or Asthmatics

* There were no differences between Healthy Controls and Asthmatics in any of the MBW tests

3b) FOT

Value	Group	Pre-bronchodilator	Post-bronchodilator	Difference Pre and Post¶,*	*P* ¶
R10 (hPa/L/sec)	Healthy Controls	7.95 (7.00, 8.84)	6.02 (5.43, 7.04)	-1.29 (-2.45, -1.02)	<0.0001
	Asthmatics	7.83 (6.76, 9.32)	6.46 (5.06, 6.97)	-1.46 (-1.99, -0.85)	<0.0001
R6-R20 (hPa/L/sec)	Healthy Controls	1.74 (0.97, 2.58)	0.92 (0.35, 1.72)	-0.73 (-0.11, -1.56)	<0.0001
	Asthmatics	2.42 (1.76, 3.39)	0.82 (0.38, 1.52)	-1.41 (-1.09, -2.62)	<0.0001
X6 (hPa/L/sec)	Healthy Controls	-3.64 (-4.92, -2.91)	-2.74 (-3.42, -2.32)	0.84 (1.64, 0.40)	<0.0001
	Asthmatics	-3.85 (-5.30, -2.77)	-2.35 (-3.61, 2.13)	1.24 (1.95, 0.41)	<0.0001
X10 (hPa/L/sec)	Healthy Controls	-2.95 (-3.62, -2.00)	-1.77 (-2.12, -1.23)	0.99 (0.59, 1.56)	<0.0001
	Asthmatics	-3.15 (-4.02, -2.39)	-1.73 (-2.08, -1.26)	1.41(1.09, 2.06)	<0.0001
f_0 (Hz)	Healthy Controls	25.21 (21.42, 28.90)	20.51 (17.83, 22.36)	-4.69 (-7.34, -2.30)	<0.0001
	Asthmatics	25.57 (22.23, 29.97)	20.50 (18.62, 22.24)	-4.01 (-8.57, -1.31)	0.0001
Rf_0 (hPa/L/sec)	Healthy Controls	6.73 (5.39, 7.60)	5.34 (4.42, 6.60)	-0.91 (-1.67, -0.71)	<0.0001
	Asthmatics	6.26 (5.46, 7.06)	5.46 (4.10, 6.67)	-0.68 (-1.02, -0.34)	<0.0001
AX (cmH_2O/L)	Healthy Controls	37.07 (27.69, 54.54)	23.61 (14.75, 27.24)	-13.8 (-26.8, -7.68)	<0.0001
	Asthmatics	42.75 (28.36, 59.27)	20.16 (14.51, 27.54)	-19.0 (-36.3, -11.9)	<0.0001

¶ There were significant changes in FOT parameters in both Healthy Controls and Asthmatics after bronchodilator administration.

* There were no significant differences in bronchodilator response between Healthy Controls and Asthmatics. The R6-R20 bronchodilator response between asthmatics and controls came closest to significantly different, however ($P = 0.058$)

the resonance frequency between healthy controls and asthmatics. They found a larger difference was found in more "persistent wheezers" than in "early wheezers", who presumably had less airway reactivity. Song et al[12] found that there was a baseline difference between healthy controls and asthmatics at only one resistance parameter, R10 Hz. All other measured baseline values did not reveal a significant difference between healthy controls and asthmatics.[12]

Previous studies have found that both healthy controls and asthmatics have a detectable response to bronchodilator administration, as measured by FOT. Thamrin[13,14] and Hellinckx[15] found that healthy controls and asthmatics had a similar degree of bronchodilator response. Oostveen's group also found that while all subjects had a bronchodilator response that was measurable by FOT, "persistent wheezers" had a larger response than any other group.[17] In Song's study all subjects had a detectable response to bronchodilator administration, with asthmatics having a larger decrease in airway resistance post-bronchodilator at 5, 10, 20, and 35 Hz.[12] Calogero et al[19] correlated bronchodilator response measured by FOT with sex and height in healthy children. At this time, there remains no standard values for degree of bronchodilator response in asthmatics versus controls.[20]

This study complements and extends these prior studies by being the first to directly compare FOT and MBW in the evaluation of baseline and post-bronchodilator lung function in preschool asthmatic children. Our results suggest that healthy controls and well asthmatics (despite their poor control) have similar characteristics of gas mixing, and similar airway mechanics, both before and after bronchodilation, and that they cannot be differentiated by either test method.

MBW measures the degree of ventilation inhomogeneity. MBW has been used extensively in children with cystic fibrosis (CF) showing good ability to measure their lung function over time.[9,11] Even though our subjects were identified as "poorly controlled" as per the C-ACT, one of the major exclusion criteria was that children had to be well and not in the midst of an asthma exacerbation. Thus, we have shown that poorly controlled asthmatics, when well, have similar gas mixing properties to healthy controls. Additionally, nearly all of the poorly controlled asthmatics were on long-term inhaled corticosteroids (ICS) or combined long acting beta agonist/inhaled corticosteroids (LABA/ICS). These medications decrease airway inflammation, and could have a beneficial effect on gas mixing, making poorly controlled asthmatics ventilation homogeneity similar to healthy controls. Children with CF have a less transient, more progressive disease course than children with asthma. Thus, children with CF are more likely to exhibit significant ventilation inhomogeneity reflected in higher LCI values and ranges.

FOT measures airway mechanics. Similar to MBW, FOT did not distinguish asthmatics from controls. However it did reveal significant responses to bronchodilator administration. Despite all subjects having a measurable response and improved airway mechanics post-bronchodilator, this response was not significantly different between healthy controls and poorly controlled asthmatics. The only parameter showing a tendency to more responsiveness to bronchodilator in the asthmatics compared to controls was the R6-R20. This is likely explained by this measurement being most sensitive to small airway function, as it subtracts central airway resistance (R20) from total airway resistance (R6), and points out the need for further evaluation of this parameter in future studies.

The similarity in bronchodilator responsiveness between asthmatics and controls is surprising, but may be because the majority of our asthmatic group were treated with maintenance medications. In addition, asthmatics, even when poorly controlled, may not have as high baseline impedance to airflow when they are not in the midst of an asthma flare, and therefore their bronchodilator responses may be more limited.

Importantly, we found that FOT is a better test of bronchodilator responsiveness than MBW. We consider two possibilities for why this may be so. First, FOT is a measure of airway mechanics, which are directly affected by the reduction in airway resistance caused by bronchodilators. Ventilation homogeneity is also impacted by airway mucous secretion and inflammation, which are slower to resolve. Second, prior studies in adults have suggested a time dependence of bronchodilator response, more rapid in central than in peripheral airways.[21] FOT may be more sensitive to central airway mechanical responses to bronchodilators than MBW, which likely only reflects the more peripheral airways.

CONCLUSIONS

This was the first direct comparison of MBW and FOT and their ability to differentiate between poorly controlled asthmatics (when well) and healthy controls; as well as their ability to detect a response to bronchodilator administration. MBW was unable to differentiate between poorly controlled asthmatics and healthy controls based on their baseline LCI, and was also unable to detect a significant bronchodilator response in either subject group. FOT was also unable to differentiate between poorly controlled asthmatics and healthy controls based on their baseline airway mechanics; but, in contrast to MBW, was very sensitive to bronchodilator induced changes in airway mechanics in both groups of subjects. The superiority of FOT to MBW in assessing bronchodilator responsiveness in both healthy and asthmatic preschoolers may reflect differential changes in airway mechanics and gas mixing properties in response to bronchodilators.

CONFLICT OF INTEREST

The authors declare that they have no competing interests. The opinions expressed in this manuscript are those of the authors and do not necessarily represent those of the United States Department of Defense or the United States Army.

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