

Assessment of bronchodilator responsiveness in preschool children using forced oscillations

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ABSTRACT

Background: The forced oscillation technique (FOT) requires minimal patient cooperation and is feasible in preschool children. Few data exist on respiratory function changes measured using FOT following inhaled bronchodilators (BD) in healthy young children, limiting clinical applications of BD testing in this age group. We aimed to determine the most appropriate method of quantifying BD responses using FOT in healthy young children, and those with common respiratory conditions, including cystic fibrosis (CF), neonatal chronic lung disease (nCLD), and those with a diagnosis of asthma and/or current wheeze.

Methods: A pseudorandom FOT signal (4 – 48 Hz) was used to examine respiratory resistance (Rrs) and reactance (Xrs) at 6, 8 and 10 Hz. Three to 5 acceptable measurements were made before and 15 minutes following the administration of salbutamol. Post-BD response was expressed both in absolute and relative (percentage of baseline) terms.

Results: Significant BD responses (BDR) were seen in all groups (Wilcoxon signed ranks test, $p < 0.05$). Absolute changes in BDR were related to baseline lung function within each group (linear regression, $p < 0.001$). Relative changes in BDR were less dependent on baseline and independent of height in healthy children. Those with nCLD showed a strong baseline dependence in their responses. The BDR in children with CF, asthma and wheeze (based on both group mean data and number of responders) were not greater than healthy children.

Conclusions: BD response assessed by the FOT in preschool children should be expressed as a relative change to account for the effect of baseline lung function. The limits for a positive BD response of -40% and 65% for Rrs and Xrs, respectively, are recommended.

INTRODUCTION

The forced oscillation technique (FOT) is increasingly used in preschool children to measure respiratory function, owing to its low requirement for patient cooperation and ease of measurement.[1] The technique allows measurement of the respiratory input impedance (Z_{rs}) under tidal breathing conditions. From this, resistance (R_{rs}) and reactance (X_{rs}) of the respiratory system can be obtained as a function of frequency. Response in respiratory function to a bronchodilator (BD) is routinely used as part of the clinical assessment of children with lung disease, but little information exists on BD response in preschool children with lung disease in comparison to health as quantified by FOT variables.

Other lung function methods have been used to assess BD responses in children of this age group both with and without lung disease, with mixed results. Spirometric parameters such as the FEV_1 are variably dependent on airway diameter and compliance, both of which are potentially altered by BD inhalation but have opposite effects on maximal flow.[2] The interrupter technique[3-7] has been shown to underestimate resistance, particularly in children with high baseline resistance.[8] Specific airway resistance (sRaw) obtained by whole-body plethysmography[9, 10] has also been used in this age group.

There are a number of FOT studies using impulse oscillometry[9, 11, 12] but due to the constraints of the technique, R_{rs} and X_{rs} are only reported at multiples of 5 Hz, thus missing out on information from other frequencies. Studies in patients with cystic fibrosis (CF) have been made using pseudorandom FOT, which have no such frequency constraints, but unfortunately had no healthy group for comparison.[2] School-aged children with neonatal chronic lung disease (nCLD) have been assessed using both impulse oscillometry[13] and pseudorandom FOT,[14] but preschool children were not included, and the assessment did not include their BD response. Mazurek and colleagues[15] used the head generator technique to perform pseudorandom FOT on asthmatic and CF patients, but only reported R_{rs} and X_{rs} data from 10 and 20 Hz, whereas Delacourt and coworkers[8] used the extrapolated parameter R_0 as an outcome variable. More recent FOT studies assessing BD responses using FOT in healthy and asthmatic children,[9, 11, 16] and in asthmatic children only,[17, 18] have employed impulse oscillometry.

The aim of this study was to characterise BD response as assessed by pseudorandom FOT in healthy preschool children, and compare this to children from different disease groups: CF, nCLD, and asthma and/or wheeze. The analysis was performed retrospectively from data collected as part of other ongoing studies. Using our findings, we aim to determine how bronchodilator responses in FOT parameters should be expressed, and what constitutes a significant bronchodilator response.

METHODS

Subjects

Healthy children were defined as those who have had no history of asthma or wheeze ever, and have not been diagnosed with CF or nCLD. They were studied at a time when they were well and had no respiratory infections in the two weeks prior to the date of study. As part of a separate study they also underwent skin prick testing to locally-relevant aeroallergens (house dust mite, cat, grass mix, mould mix) and their parents answered a questionnaire which yielded

information on respiratory history and environmental tobacco smoke exposure. Atopy was defined as a positive skin prick test to one or more allergens, where a positive result was determined by a wheal diameter of at least 3 mm after 15 minutes.

Children with CF and nCLD were measured as part of clinical follow-up programs at the Princess Margaret Hospital for Children. Children with CF were identified through neonatal screening, or from clinical criteria and confirmed by sweat electrolyte analysis. Children with nCLD were those who required use of supplemental oxygen for more than 28 days at 36 weeks postmenstrual age for infants with gestational age (GA) at birth of less than 32 weeks and the use of supplemental oxygen at 28 days of life for individuals with GA at birth \geq 32 weeks.[19] Current wheeze was defined by the occurrence of episodes of wheezing in the past 12 months. Children with asthma were those with current wheeze who also had a doctor diagnosis of asthma.

Measurements were made in children when neither long-acting bronchodilator had been administered for at least 24 hours, nor short-acting bronchodilator for at least 4 hours, prior to the testing session. Subject anthropometrics are shown in Table I.

Forced oscillation technique

The FOT methods used in this study have been previously described and validated.[20] Respiratory impedance spectra (Zrs), yielding Rrs and Xrs as a function of frequency, were obtained using commercially-available equipment (I2M, Chess Medical, Belgium) based on the specifications of Lándsér and coworkers,[21] in accordance with ERS guidelines.[1] The forced oscillatory signal was a pseudorandom signal consisting of frequency components between 4 – 48 Hz, with a measurement period of 8 seconds.

Protocol

During measurement, the child was seated comfortably upright, with the neck in the neutral position and the arms resting comfortably by the side. The child's cheeks were supported by an investigator. Measurements were made with the child wearing a nose-clip during quiet breathing through a mouthpiece and filter (Suregard, BirdHealthcare, Australia).

Three to five technically acceptable measurements were obtained at baseline. Individual measurements were considered technically unacceptable if coherence was <0.95 at three or more frequencies or if Zrs showed obvious artifacts.

Salbutamol (600 μg) was administered via a pressurised metered-dose inhaler (Ventolin, GlaxoSmithKline) and spacer device (Volumatic, GlaxoSmithKline). Respiratory function measurements were repeated (as above) 15 minutes post-BD inhalation. All protocols used in this study were approved by the Ethics Committee at the Princess Margaret Hospital for Children and parental consent was obtained.

Data analysis

All technically acceptable Zrs measurements were averaged and mean Rrs and Xrs at 6, 8, and 10 Hz (Rrs₆, Rrs₈, Rrs₁₀, Xrs₆, Xrs₈, and Xrs₁₀, respectively) calculated. Both absolute and relative BD responses were studied, where the relative BD response was the absolute BD response expressed as a percentage of baseline respiratory function.

With the BD response assessed by each FOT variable as the outcome, multiple linear regression analysis was performed, stratified by disease group, to determine the individual effects of the following factors on absolute and relative BD responses within each group: age, gender, height, weight, baseline lung function. These covariates were then also adjusted for in a multiple linear regression model used to compare the BD response in each disease group to the healthy group. All statistical analyses were performed at $\alpha = 0.05$, using customised software (Intercooled Stata 8.1 for Windows, Stata Corporation, Texas, USA). Significance was defined as $p < 0.05$.

RESULTS

Baseline and BD responses

Anthropometric data and baseline respiratory function are shown in Table I. Children with nCLD were shorter and lighter than other children, most likely explaining the higher resistance and lower reactance at all frequencies compared to healthy children. Children with CF also had higher resistance (all frequencies) and lower reactance (at 6 Hz) (Table I). There were no differences in baseline respiratory function between the children with asthma or wheeze and the healthy children (Table I). In all groups, lung function post-bronchodilator significantly improved compared to baseline, i.e. the resistance parameters decreased while the reactance parameters increased (Figure 1, Wilcoxon signed ranks test, $p < 0.05$ for all variables).

Table I. Subject anthropometrics and baseline lung function. Continuous data are represented as the median (10th, 90th percentile). Numbers in bold indicate a significant difference compared to the healthy group (Mann-Whitney test for each group, $p < 0.05$).

	Healthy (78)	CF (39)	nCLD (49)	Asthma (56)	Wheeze (66)
Age [mth]	61 (50, 62)	60 (43, 80)	62 (43, 71)	61 (47, 80)	61 (49, 80)
Sex [M:F]	36:42	15:24	23:26	35:21	41:25
Ht [cm]	110 (103, 118)	107 (94, 122)	106 (96, 113)	112 (101, 123)	112 (102, 122)
Wt [kg]	19.5 (15.8, 22.6)	17.8 (14.2, 24.7)	16.4 (13.9, 19.9)	20.0 (15.7, 26.3)	20.0 (16.0, 25.1)
Baseline lung function					
Rrs ₆ [hPa L ⁻¹ s]	7.69 (5.53, 11.78)	9.03 (6.66, 11.30)	11.12 (8.16, 14.29)	8.17 (5.67, 13.06)	8.03 (5.65, 12.84)
Xrs ₆ [hPa L ⁻¹ s]	-2.83 (-4.88, -1.36)	-3.51 (-5.23, -2.24)	-4.90 (-6.78, -3.43)	-3.18 (-5.67, -1.44)	-3.12 (-5.44, -1.42)
Rrs ₈ [hPa L ⁻¹ s]	7.58 (5.54, 10.68)	8.94 (6.45, 11.34)	10.49 (7.61, 13.31)	8.06 (5.69, 13.08)	7.84 (5.66, 12.69)

Xrs ₈ [hPa L ⁻¹ s]	-2.44 (-4.52, -1.51)	-2.82 (-5.66, -1.50)	-4.08 (-5.74, -2.73)	-2.50 (-5.55, -1.01)	-2.35 (-5.10, -1.13)
Rrs ₁₀ [hPa L ⁻¹ s]	7.17 (5.44, 10.37)	8.32 (6.15, 10.52)	9.66 (7.19, 11.79)	7.67 (5.47, 11.80)	7.42 (5.42, 11.36)
Xrs ₁₀ [hPa L ⁻¹ s]	-2.57 (-4.65, -1.46)	-2.75 (-5.10, -1.40)	-4.03 (-5.86, -2.46)	-2.44 (-5.28, -1.04)	-2.46 (-5.24, -1.06)

Approximately one third (24/78) of the healthy group were atopic and 17.9% (14/78) were exposed to tobacco smoke. Neither atopy nor passive smoke exposure influenced baseline lung function, absolute or relative BD responses measured by any of the FOT variables (Mann-Whitney test, $p > 0.05$ for all tests).

Dependence of BD responses on anthropometric factors and baseline lung function

Stratified for disease group, the absolute response measured by all FOT variables was found to be strongly dependent on baseline lung function ($p < 0.001$). The absolute response was not dependent on any of the other factors, in any of the groups studied, with the exception of Rrs₆ vs age in the healthy group (coeff. = -0.058, $p = 0.017$), Xrs₆ vs age and sex in the CF group (coeff. = -0.046, $p = 0.010$, and coeff. = 0.520, $p = 0.039$, respectively), Xrs₈ vs weight in the nCLD group (coeff. = -0.150, $p = 0.027$), and Xrs₁₀ vs height in the wheeze group (coeff. = 0.072, $p = 0.026$). Scatter graphs for Rrs₈ and Xrs₈ plotted against baseline (Fig. 2) were representative of the relationships between FOT variables and baseline in general.

Stratified for disease group, the relative response measured by all FOT variables was less significantly dependent on baseline lung function (significant p values ranging from <0.001 to 0.45), with no relationship found between baseline and Rrs₈, Rrs₁₀ or Xrs₆ in the healthy group, and Rrs₁₀ in the CF group. In addition, Xrs₆ vs age in the CF group (coeff. = -1.14, $p = 0.036$), Xrs₈ vs weight in the nCLD group (coeff. 4.11, $p = 0.020$), and Xrs₁₀ in the wheeze group (coeff. 2.67, $p = 0.018$) were also found to be significant.

Comparison of relative BD responses between healthy and disease groups

Results from comparisons between healthy and disease groups, adjusted for age, sex, height, weight and baseline, were similar for the absolute (Table II) and relative (Table III) BD responses. For the sake of simplicity, only the relative responses are described here.

Table II. Absolute bronchodilator responses. Data shown as median absolute change with bronchodilator (10th, 90th percentile). Numbers in bold indicate a significant difference compared to the healthy group (Multiple linear regression for each group, adjusted for covariates, $p < 0.05$).

	Healthy (78)	CF (39)	nCLD (49)	Asthma (56)	Wheeze (66)
ΔRrs_6 [hPa s L ⁻¹]	-1.51 (-3.69, -0.17)	-1.46 (-3.18, -0.04)	-2.44 (-4.14, -0.98)	-1.17 (-4.10, 0.58)	-1.28 (-4.03, 0.51)
ΔXrs_6 [hPa s L ⁻¹]	0.57 (-0.27, 1.66)	0.86 (-0.16, 2.05)	1.49 (0.15, 3.05)	0.84 (-0.21, 2.30)	0.84 (-0.14, 2.33)
ΔRrs_8 [hPa s L ⁻¹]	-1.44 (-2.73, -0.30)	-1.30 (-3.13, 0.28)	-1.94 (-3.78, -0.54)	-1.09 (-3.39, 0.59)	-1.09 (-3.39, 0.53)
ΔXrs_8 [hPa s L ⁻¹]	0.75 (-0.04, 1.82)	0.75 (-0.17, 2.06)	1.51 (0.47, 2.98)	0.79 (-0.13, 2.47)	0.79 (-0.13, 2.47)
ΔRrs_{10} [hPa s L ⁻¹]	-1.34 (-2.55, -0.21)	-1.24 (-2.62, 0.30)	-1.76 (-3.03, -0.46)	-0.89 (-2.90, 0.29)	-0.95 (-2.90, 0.24)
ΔXrs_{10} [hPa s L ⁻¹]	0.73 (-0.00, 2.03)	0.73 (0.00, 1.99)	1.61 (0.36, 3.08)	0.67 (-0.12, 2.22)	0.71 (0.00, 2.14)

Table III. Relative (% baseline) bronchodilator responses. Data shown as median relative change with bronchodilator (10th, 90th percentile). Numbers in bold indicate a significant difference compared to the healthy group (Multiple linear regression for each group, adjusted for covariates, $p < 0.05$).

	Healthy (78)	CF (39)	nCLD (49)	Asthma (56)	Wheeze (66)
ΔRrs_6 [%]	-21.3 (-35.0, -3.1)	-16.8 (-32.1, -0.6)	-23.3 (-33.0, -9.2)	-14.9 (-37.0, 8.8)	-16.0 (-37.9, 8.4)
ΔXrs_6 [%]	27.4 (-7.5, 50.0)	23.5 (-5.1, 46.7)	31.9 (4.0, 49.8)	27.0 (-13.8, 57.3)	28.4 (-6.5, 59.9)
ΔRrs_8 [%]	-18.7 (-35.0, -4.4)	-14.8 (-26.7, 4.1)	-19.2 (-33.0, -5.2)	-16.0 (-33.1, 9.7)	-16.3 (-33.1, 8.9)
ΔXrs_8 [%]	30.9 (-1.6, 62.6)	30.0 (-6.5, 56.1)	38.8 (16.4, 63.2)	30.3 (-7.8, 58.9)	32.2 (-7.8, 60.9)
ΔRrs_{10} [%]	-18.8 (-32.3, -3.7)	-15.0 (-26.8, 4.3)	-18.2 (-27.5, -4.9)	-14.7 (-33.4, 4.5)	-15.3 (-33.4, 3.0)
ΔXrs_{10} [%]	29.3 (-0.2, 53.9)	29.4 (0.3, 53.6)	35.5 (14.3, 56.9)	32.7 (-7.0, 57.5)	33.9 (0.0, 58.4)

As a group, children with CF tended to have smaller relative BD responses compared to healthy in general. Adjusted for covariates, Rrs_8 and Rrs_{10} were found to be significantly different to the healthy group (adjusted $p = 0.031$ and $p = 0.021$, respectively). There were no significant differences in relative BD assessed by any of the FOT parameters between CF patients who had (53%) or did not have (47%) respiratory symptoms (parental reported cough, cold or sputum production, or clinician reported wheeze, crackles or respiratory tract infection) at the time of the study.

Children with nCLD as a group tended to have larger relative BD responses compared to healthy in general, with Rrs_8 and Rrs_{10} found to have a weakly-significant difference to healthy (adjusted $p = 0.045$ and 0.042 , respectively). In this group, baseline remained a significant covariate in the multiple linear regression model, for all FOT variables.

Children with a doctor diagnosis of asthma showed significant differences to the healthy group in terms of BD responses assessed by Rrs_6 , Rrs_8 and Rrs_{10} (adjusted $p = 0.008$, 0.004 , and 0.002 , respectively) but not by any of the Xrs variables. Similar results with weaker significance were seen in children with wheeze (adjusted $p = 0.049$, 0.010 , and 0.004 , respectively for Rrs_6 , Rrs_8 and Rrs_{10}). In this group, Rrs responses tended to be smaller compared to healthy, while Xrs responses tended to be larger, though again the latter were not significant.

Significant relative BD response

The characteristics of the healthy group were used to determine what constitutes a significant BD response. As BD response was significantly dependent on baseline lung function these analyses were only undertaken using relative BD responses. To the nearest percentage change, the limits of agreement for relative BD responses in the healthy group were set to be -42% , -37% , and -39% for Rrs_6 , Rrs_8 and Rrs_{10} , respectively (taken from the 5th percentiles), and 61% , 67% , and 63% for Xrs_6 , Xrs_8 , and Xrs_{10} , respectively (taken from the 95th percentiles).

Using these criteria, the number of subjects who responded significantly to BD, i.e. who had a response greater than these limits, was counted within each of the disease groups (Table IV). While the number of responders in each disease group did not differ significantly in comparison to the healthy group (Fisher's exact test, $p > 0.05$), the reactance parameters tended to yield more responders than the resistance parameters.

Table IV. No of subjects in each group showing a significant relative bronchodilator response as determined by the limits of the healthy group for resistance (Rrs) and reactance (Xrs) at 6, 8 and 10 Hz.

	Healthy	CF	nCLD	Asthma	Wheeze
$ \Delta Rrs_6 > 42\%$	3/68 (4.4%)	0/36 (0.0%)	1/49 (2.0%)	2/53 (3.8%)	3/61 (4.9%)
$ \Delta Xrs_6 > 61\%$	3/68 (4.4%)	1/36 (2.8%)	0/49 (0.0%)	2/53 (3.8%)	5/61 (8.2%)
$ \Delta Rrs_8 > 37\%$	3/78 (3.8%)	1/38 (2.6%)	2/49 (4.1%)	1/55 (1.8%)	2/65 (3.1%)
$ \Delta Xrs_8 > 67\%$	4/78 (5.1%)	2/38 (5.3%)	2/49 (4.1%)	2/55 (3.6%)	3/65 (4.6%)
$ \Delta Rrs_{10} > 39\%$	3/78 (3.8%)	0/38 (0.0%)	0/49 (0.0%)	1/56 (1.8%)	1/66 (1.5%)
$ \Delta Xrs_{10} > 63\%$	3/78 (3.8%)	1/38 (2.6%)	3/49 (6.1%)	2/56 (3.6%)	2/66 (3.0%)

DISCUSSION

The results of the present study demonstrate that the magnitude of the change in lung function following BD inhalation, measured with pseudorandom FOT, in preschool children is strongly related to baseline lung function. This is true for healthy children and those with lung disease. Reporting BD responses relative to baseline lung function, i.e. as a percent of baseline, accounts for this effect to some extent.

Characterisation of BD responses

The magnitude of the BD responses presented in this study at 6 and 10 Hz (-21% for Rrs_6 and 27% for Xrs_6 , and -19% for Rrs_{10} and 29% for Xrs_{10}) compare well to data measured using impulse oscillometry at 5 and 10 Hz published by Malmberg and coworkers,[12] who reported a change of -19.2% for Rrs_5 and -19% for Rrs_{10} . They also reported a change of 0.64 and 0.60 hPa s L⁻¹ for Xrs_5 and Xrs_{10} , respectively (relative changes not provided), similar to the 0.57 and 0.73 hPa s L⁻¹ for Xrs_6 and Xrs_{10} , respectively seen in our study. In contrast, Hellinckx and colleagues[11] (-13% for Rrs_5 and 15% for Xrs_5), and Nielsen and Bisgaard[9] (-10% for Rrs_5 and 14% for Xrs_5) both reported smaller changes in lung function following BD inhalation. There was a large spread of BD responses in our groups, as was the case in the other previously published studies.

Our finding that BD response as assessed by FOT parameters at 6, 8 and 10 Hz is related to its corresponding value at baseline is consistent with that of Hellinckx and coworkers[11] who also found correlation between absolute BD response and baseline lung function in total Rrs and Xrs . [22][23] [16]

While baseline lung function is generally known to be dependent on height, we found that BD response as measured by FOT variables was height-independent (with the exception of Xrs_{10} in wheeze), irrespective of whether it is expressed as an absolute or a relative response.

The children were generally studied at times when they were clinically stable and generally asymptomatic. The purpose for including children from the various disease groups was to determine whether the underlying disease increased the short term variability of FOT. In general, our data shows that criteria for determining BD response in healthy children are also valid for children with CF, nCLD, asthma and current wheeze. There is a suggestion from our data that FOT parameters at 6 Hz, specifically Xrs_6 , may be the most appropriate for expressing BD response in preschool children. Reactance has been shown to be a more sensitive indicator of airway obstruction.[22, 23] It is plausible that this applies to reversibility of airway obstruction as well.

Based on results from our healthy group, the criteria for defining a significant BD response are similar for both Rrs and Xrs at 6, 8 and 10 Hz (Table V). A fall in Rrs of 40% and an increase in Xrs of 65% appear to be suitable criteria for defining a BD response. Our data do show that the 6 Hz data point was more often unavailable due to low coherence (55/252, 21.8%) than either the 8 Hz (40/252, 15.9%) or the 10 Hz (39/252, 15.5%) data point. Thus Rrs_8 and Xrs_8 may offer the best balance between sensitivity and reliability for assessing BD responses in preschool children. The BD criteria proposed here are similar to those previous suggested in studies using impulse oscillometry. Hellinckx and coworkers[11] set the cut-off for Rrs_5 at -41%. Similarly, Malmberg and coworkers[12] proposed -37% and -34% as cut-offs for Rrs_5

and Rrs_{10} , respectively. Nielsen and Bisgaard[9] found the 5th percentile for BD response in Rrs_5 to be much lower at -28%. The corresponding cut-off for Xrs_5 was -42%.

Cystic fibrosis

As a group, the CF children in this study did not exhibit a greater BD response in resistance, and showed no difference in BD response in reactance, compared to healthy children. We also found that there were no significant differences in the number of responders between health and CF, irrespective of symptomatic status. This compares well with a longitudinal study by Nielsen and coworkers[10], where no differences in bronchodilator responsiveness were demonstrated between healthy children and children with CF as measured by sRaw. The authors also looked at impulse oscillometry and found Xrs_5 to yield a statistically significant greater BD response in CF but dismissed this as a type I error. Note that when using the Z-score for Xrs_5 as a criterion, the authors found 20% of CF children exhibited a positive BD response on their first visit and 16% on their second visit. However, none of the FOT results were expressed as relative changes (the FOT results were expressed as an absolute change in Z-score), and so any effects of baseline magnitude were not adjusted for. In another study, Hellinckx and coworkers[2] looked at Rrs_6 and determined that 13 out of 20 CF patients had a favourable response to BD, but used a cut-off of -12% obtained from the within-subject variability of the CF group itself, which was much smaller than the limits of the BD response used in this study.

Neonatal chronic lung disease

To our knowledge, no FOT data on BD response in preschool children with nCLD have been published. Our data show that even when expressed as a percentage of the higher baseline values, BD responses in nCLD tend to be larger than those in healthy children, and still showed a significant dependence on baseline respiratory function. Baseline was found to be a particularly strong covariate in this disease group, and was also largely responsible for any apparent differences in the BD response. This is perhaps not surprising given the difference in height and weight between the nCLD children and the healthy group. In effect, we conclude that there were no differences in BD response between the healthy and nCLD children we studied. A previous study[24] found school-aged children with nCLD to have significantly higher BD responsiveness than controls, as assessed using spirometry. We are unaware of equivalent studies in preschool children to enable us to compare any differences that may be revealed between spirometry and FOT.

Asthma/wheeze

On grouped data, the BD response assessed by the Rrs variables were not larger in the asthma or wheeze groups compared to healthy children, and in fact tended to be smaller when adjusted for covariates. There were no significant differences in the BD response assessed by the Xrs variables. Hellinckx and coworkers[11] found no differences in BD responses at Rrs_5 and Rrs_{10} between healthy children and stable asthmatic children who had normal baseline lung function. When considered as individuals, more wheezy children in our study had a BD response outside the limits of the healthy group when this response was assessed using Xrs_6 . Only 11 out of the 66 children in the wheeze group did not have persistent wheeze (defined in this case by wheeze prior to the past 12 months in addition to within the past 12 months), indicating that these children probably had asthma despite a lack of diagnosis from a doctor. However, all children were asymptomatic at the time of lung function studies. Thus the lack of differences in baseline

lung function and in BD responses between these children and the healthy group are not surprising. One study using the interrupter technique have shown increased BD responses in wheezy preschool children compared to past wheezers,[25] however this involved children who had a recent exacerbation and were likely to be more severely asthmatic than our asthma group. Another interrupter study found a great degree of overlap between asthmatic and healthy preschool children, although the dosage used was much lower than that used in our study[6]. There is also a possibility that the higher dosage used in our study, which is normally used for bronchodilator testing in our laboratory, contributed to the differences to these and other previous studies. Furthermore, it should be pointed out that some of the children in our asthmatic or wheeze group would have been on inhaled corticosteroids. Characterisations of the BD response in symptomatic and asymptomatic asthma, or in children from whom inhaled corticosteroids are withheld, are beyond the scope of the present study.

In summary, the data from the present study show that the magnitude of BD responses in preschool children measured using pseudorandom FOT is strongly influenced by baseline lung function. Thus changes in lung function should be reported as a percent of baseline to alleviate this effect. The best balance between responsiveness and reliability appears to be provided by Rrs_8 and Xrs_8 . A fall in Rrs of 40% or an increase in Xrs of 65% are indicative of significant changes in respiratory function following BD inhalation. Further systematic studies are required to determine the clinical significance of post BD changes in lung function in preschool children with lung disease.

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COMPETING INTERESTS

All authors declare that the answer to the questions on the competing interest form bmj.com/cgi/content/full/317/7154/291/DC1 are all No and therefore have nothing to declare.

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FIGURE LEGENDS

Figure 1. Pre- and post-bronchodilator responses in all groups measured by resistance (Rrs) and reactance (Xrs) at 6, 8 and 10 Hz. Open circles and squares indicate outliers and extreme values, respectively. In all parameters, post-bronchodilator responses (patterned boxplots) were significantly different compared to pre-bronchodilator responses (non-patterned boxplots) in all groups (Wilcoxon signed ranks test, $p < 0.05$).

Figure 2. Absolute bronchodilator response plotted against baseline for resistance (Rrs) and reactance (Xrs) at 8 Hz. Different symbols indicate different groups (Circle: Healthy; Rectangle: CF; Triangle up: nCLD; Triangle down (solid): Asthma; Triangle down (open): Wheeze only).

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