APJAI
Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

Early detection of airway obstruction by impulse oscillometry system in methacholine challenge testing in preschool children

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Abstract

Background: Small airway hyperresponsiveness is a critical aspect in preschool children with asthmatic symptoms in terms of asthma control. The aim of this study was to elucidate the relationship of changes in reactance (Xrs) and resistance (Rrs) of IOS and FEV_1 with those in clinical parameters and to determine which IOS parameter is correlated with bronchial hyperresponsiveness before positive clinical endpoints.

Methods: We performed the methacholine challenge test in ninety-four preschool children (4.2 ± 1.1 years) with suspected asthma. The end of test (EOT^+) was defined as one or more of the following: audible wheezing (PCw^+), a fall in the oxygen saturation (< 92%, PCs^+) or development of respiratory symptoms (PCr^+).

Results: Mean changes in FEV_1, Xrs_5, and Rrs_5 in the EOT^+ group were 39.2 ± 14.3% (95%CI 35.1-43.2%), 176.8 ± 78.0 (95%CI 154.9-198.8) and 53.6 ± 30.2 (45.1-62.0), respectively. The changes of Xrs_5 in three EOT^+ groups exceeded 80% and were lowest in PCr^+(median, 95.9, IQR; 73.4 to 132.4), followed by PCw^+ and PCs^+. However, Rrs_5 did not show greater than 40% changes in PCr^+. Xrs_5 showed a higher correlation with changes in saturation (r = -0.578) than Rrs_5 (r = -0.426). A49% decrease in Xrs_5 was the optimal point for predicting a 80% change of Xrs_5 at the following step.

Conclusion: When examining the 5 step methacholine challenge test in preschoolers, the use of clinical parameters alone as an endpoint is of little value. The reactance value of 5 Hz is a useful predictive marker for bronchial hyperresponsiveness.

Key words: Impulse Oscillation, Dose-response Slope, Bronchial hyperresponsiveness, Spirometry, auscultation method

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Background

Measurements of bronchial hyperresponsiveness (BHR) have provided integral information for the diagnosis and management of lung diseases in children and adults.[1] Forced spirometry can be feasible in preschool children, allowing evaluations of bronchodilator response[2] and baseline lung function. However, young children lack the ability to tolerate the repetitive measurements of bronchial challenge testing with spirometry and thus hindering its clinical use.[3,4] Therefore, other methods have been used clinically to assess bronchial hyperresponsiveness in preschool children, including the auscultation method,[4] transcutaneous oximetry,[5] and transcutaneous oxygen tension,[6] as well as other techniques to measure lung function, such as the forced oscillation technique (FOT),[7] the impulse oscillation system (IOS),[8] the interrupter technique,[9] and plethysmography.[10] However, these techniques have some limitations. Wheezing and cutaneous monitoring could be potentially dangerous to subjects,[6] and interrupter technique is less sensitive in determining airway caliber in asthmatic children who undergo methacholine challenge testing.[11] Body plethysmography and spirometry have lower success rates,[12] and the equipment

required for plethysmography limits its usefulness in clinical settings.[13]

Accordingly, studies using the oscillation technique to assess bronchial hyperresponsiveness in preschool children are increasing.[8,14,15] Clinical use of methacholine provocation testing with five sequential concentration is limited in young children due to difficulty of performing the challenge test correctly and the lack of criteria for positive test in differentiating the asthmatic children.

Therefore, the purpose of this study was to investigate the relationship of changes in reactance and resistance of IOS and FEV_1 with those in clinical endpoints such as oxygen saturation, auscultation and respiratory symptoms and to determine which IOS parameter is significantly correlated with bronchial hyperresponsiveness before positive clinical endpoints in preschoolers.

Methods

Subjects

We enrolled children with asthmatic symptoms such as recurrent wheezing episodes (more than twice) diagnosed at least once at the Pediatric Allergy clinic of CHA Bundang Medical Center who showed a positive bronchodilator response or improvement after taking inhaled corticosteroid between June 2010 and May 2012. The family and personal medical history of each subject were based on questionnaires, physical examinations, and lung function tests.

Methacholine challenge testing

Bronchial challenge testing was performed with 5-step quadrupling concentration doses (0.0625, 0.25, 1, 4, and 16 mg/mL methacholine dissolved in phosphate buffer). At each step, oxygen saturation, chest and tracheal auscultation, and subjective respiratory symptoms were checked by two experienced specialists and IOS pulmonary function tests were also performed. FEV_1 was measured by spirometry at baseline and at the end of the test due to concerns about exhaustion of the subject. IOS measurements were systematically taken prior to spirometry. The end point of a challenge for the EOT positive group (EOT^+) was defined as one or more of the following: (a) audible wheeze over the chest or trachea (provocation concentration of wheezing; PCW^+); (b) oxygen saturation below 91% (provocation concentration of saturation; PCS^+); or (c) respiratory symptoms such as persistent cough, shortness of breath, or tachypnea for which the children were unable to sustain the test (provocation concentration of respiratory symptoms; PCr^+).[4,5] Subjects were defined as EOT negative (EOT^-) if they reached a methacholine concentration of 16 mg/mL without developing these manifestations. Each subject inhaledsolution for 1 minute using a nebulizer (DeVilbiss Health Care Inc., Somerset, PA) and a facemask, continuing every 5 minutes until the maximum concentration or end point was reached.[4] All children were asked to abstain from bronchodilators for at least 12 h before methacholine challenge. After the methacholine challenge test, 4 puffs of salbutamol with a spacer were administered to the child. This study was approved by the Institutional Review Board of the CHA Bundang Medical Center, CHA University School of Medicine. Written informed consent was obtained from the parents or guardians of all participants following a detailed explanation of the study.

IOS

IOS was performed 30, 60, and 90 seconds after methacholine inhalation in accordance with the ATS guidelines. For quality control, we monitored the visual acceptance of volume, flow and impedance traces.[2] Participants breathed tidally into the IOS mouthpiece for at least 30seconds.

Spirometry

Spirometry was performed using a Jaeger MasterScreen device (Jaeger CO, Wurzburg, Germany), according the ATS guidelines.[16] Spirometry results in these children were compared with those of healthy children by determining z-scores.[17]

Auscultation and saturation monitoring

Auscultation was performed independently by an experienced pulmonary technician and a pediatrician (Han MY) at baseline and at each inhalationstep.[18] The methacholine concentration at which wheezing was first heard clearly over the lung by both medical professionals was defined as the result of determination by auscultation (PCW^+). Oxygen saturation (SpO_2) was monitored using a finger oximeter (GO2, Nonin Medical Inc, Biox 3700e, Minnesota, USA). The percent reduction in oxygen saturation was calculated using the following formula: 100 × (baseline saturation - post saturation) / (baseline saturation). Changes in saturation were grouped as < 2% (S1), 2-3.9% (S2), 4-5.9% (S3), 6-7.9% (S4) and ≥ 8% (S5). The mean percent reduction in oxygen saturation during bronchial challenge was approximately 3%, included in the S2 group.[19]

Calculation of cumulative dose of methacholine

Methacholine chloride (Sigma Chemical, St. Louis, MO, USA) was inhaled usinga PARI BOY nebulizer (PARI GmbH, Starnberg, Germany), with a mean output of 0.20 ± 0.02 ml/min. The dose response slope was defined as percent reduction in FEV_1 from baseline to the final dose of methacholine administered divided by the final cumulative dose.[20]

Although bronchial hyperresponsiveness is usually confirmed by measuring PC_{20}–FEV_1, the provocative concentration causing a 20% fall in FEV_1 by spirometry,[21] we were not able to calculate PC_{20}–FEV_1 accurately as FEV_1 was performed only at baseline and at the last step and described as dichotomy of positive or negative results. We therefore used the dose-response slope,[22,23] PC_{80}–Xrs_5[8,23,24] and PC_{40}–Rrs_5[14,25,26] to compare bronchial hyperresponsiveness in our EOT^+ and EOT^- groups. PC_{80}–Xrs_5 and PC_{40}–Rrs_5 positive means that the rate of change in the last step from baseline decreased by 80% or more in reactance and increased by 40% or more in resistance when measuring with IOS. The method of calculating DRS is briefly described as follows.[22,23] We obtained the cumulative dose at each level expressed in micromoles as 0.014, 0.072, 0.302, 1.222, and 4.901 mmol, respectively, which were obtained using the molecular weight of methacholine chloride (195.7 g/mol). The slope was defined as log (percent change in X/last cumulative dose), where X represents Rrs_5, Xrs_5, and FEV_1.

Statistics

Continuous variables in the EOT$^+$ and EOT$^-$ groups were compared using the independent Student's *t* tests, and categorical variables were compared using the chi squared tests. Pearson correlation analysis was used to analyze changes in SpO_2, Xrs_5, and Rrs_5. Analysis of variance testing with *post hoc* LSD analysis was used to assess differences among the S1~S5 groups. ROC curves were used to predict 80% changes in Xrs_5 at each step. All statistical analyses were performed with PASW statistical software (version 20.0; PASW Statistics; Chicago, IL, USA). All statistical tests were two-sided and statistical significance was defined as a P value < 0.05.

Results

Characteristics of subjects

The anthropometric data and baseline lung function of the subjects are presented in **Table 1**. Of 94 preschool children, 92 children (98%; 52 boys, mean age 4.2 ± 1.1 years) performed technically acceptable IOS and 75 (80%, 42 boys, mean age 4.4 ± 1.0 years) performed technically acceptable spirometry; of the latter, three children completed baseline spirometry, but failed to perform spirometry at the last step.

Comparison of EOT$^+$ and EOT$^-$ children

Of the 72 children who successfully completed FEV_1, 51 (70.8%, mean age 4.4 ± 1.1 years) had a positive EOT (EOT$^+$) and 21 (29.2%, mean age 4.7 ± 1.0 years) had a negative EOT (EOT$^-$). There were no differences in age and gender between groups. The percent change, z score, and DRS of FEV_1 were statistically different between groups, but the IOS test showed no significant difference except for DRS result (**Table 2**). Both DRS Xrs_5 (r = 0.864, P < 0.001) and DRS Rrs_5 (r = 0.836, P < 0.001) showed strong positive correlations with DRS FEV_1 (**Figure 1**). Moreover, DRS of Rrs_5 and Xrs_5 were strongly correlated with each other (r = 0.911, P < 0.001).

Table 1. Demographic characteristics and baseline lung function

	N = 94
Age, years (95%CI)	4.2 (3.9, 4.4)*
Gender, boy/girl	54 / 40
Height, cm (95%CI)	107.4 (105.7, 109.1)*
Parental asthma, n (%)	7 (7)
Atopic dermatitis, n (%)	19 (20)
Allergic rhinitis, n (%)	38 (40)
Secondary smoking (%)	51 (54)
Impulse oscillometry (n = 92)	
Xrs_5, actual, kPa/L/sec (95%CI)	-0.44 (-0.41, -0.47)
Z score	-0.86 (-0.77, -0.96)
Rrs_5, actual, kPa/L/sec (95%CI)	1.14 (1.09, 1.19)
Z score	-1.39 (-1.09, -1.69)
Spirometry (n = 72)	
FEV_1, % predicted (95%CI)	100.8 (97.7, 104.0)
Z score, (95%CI)	0.37 (0.07, 0.67)
FEV_1/FVC, % (95%CI)	92.2 (91.0, 93.4)

Table 2. Lung function test between EOT$^+$ and EOT$^-$ group in the 72 subjects

	EOT$^+$ group n = 51	EOT$^-$ group n = 21	*P* value
Demographics			
Age, years (SD)	4.4 (1.1)	4.7 (1.0)	0.205
Gender, male (%)	31 (60.8)	9 (42.9)	0.164
Height, cm (SD)	108.7 (8.2)	109.7 (8.1)	0.641
FEV_1			
PC20 positive, n (%)	47 (92.2)	19 (90.5)	0.569
%change (95%,CI)	39.2 (35.1, 43.2)	30.9 (26.1, 35.6)	**0.019**
Z score (95%,CI)	-3.82 (-3.38, -4.26)	-2.81 (-2.23, -3.39)	**0.010**
DRS, (95%,CI)	1.34 (1.17, 1.51)	0.57 (0.50, 0.64)	**< 0.001**
IOS_Xrs_5			
PC80 positive, n (%)	47 (92.2)	16 (76.2)	0.075
%change (95%,CI)	176.8 (154.9, 198.8)	159.2 (119.0, 199.4)	0.404
Absolute change, kPa/L/s	-0.72 (0.81-0.63)	-0.61 (0.77-0.45)	0.213
Z score	-3.53 (-3.14, -3.92)	-3.07 (-2.44,-3.71)	0.212
DRS (95%,CI)	1.99 (1.83, 2.16)	1.18 (0.98, 1.37)	**< 0.001**
IOS_Rrs_5			
PC40 positive, n (%)	34 (66.7)	16 (76.2)	0.425
%change (95%,CI)	53.6 (45.1, 62.0)	53.2 (42.4, 63.9)	0.958
Abs change, kPa/L/s	0.57 (0.49-0.64)	0.56 (0.46-0.67)	0.975
Z score	-5.24 (-4.66. -5.83)	-5.12 (-4.25, -5.99)	0.809
DRS (95%,CI)	1.45 (1.30, 1.61)	0.77 (0.66, 0.89)	**< 0.001**

EOT, end of test; IOS, impulse oscillation system; DRS, dose response slope;
PC_{20}–FEV_1, PC_{80}–Xrs_5 and PC_{40}–Rrs_5 positive mean that the rate of change in the last step from baseline decreased by 20% or more in FEV_1 when measuring by spirometry, decreased by 80% or more in reactance and increased by 40% or more in resistance when measuring by IOS.
%change means that the rate of change in the last step from baseline of FEV_1, Xrs_5 and Rrs_5 during methacholine challenge test.

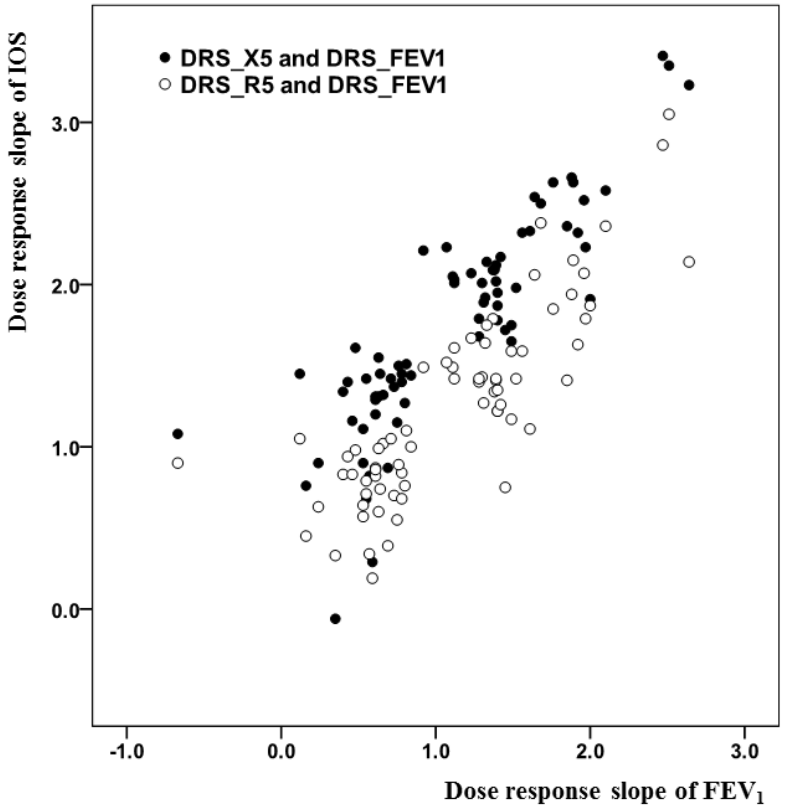

Figure 1. Correlation among the dose response slopes (DRS) of FEV_1, Rrs_5 and Xrs_5. DRS_FEV_1 showed a stronger correlation with DRS_Xrs_5 (r = 0.864, $P < 0.001$) than with DRS_Rrs_5 (r = 0.836, $P < 0.001$).

Comparison of lung parameters between PCw⁺, PCs⁺, and PCr⁺

Among the EOT⁺ subjects, there were 25 children in PCw⁺, 10 children in PCs⁺, 9 children in PCr⁺, and 26 children who showed wheeze and other conditions. The results of the lung function tests in the three groups for the reasons of discontinuation are shown in **Table 3**. The change of the reactance value was the lowest in PCr⁺ (median, 95.9, IQR; 73.4 to 132.4), followed by PCw⁺ (median 151.3, IQR 78.2 to 203.8) and PCs⁺ (median 232.7, IQR 207.0 to 273.7) ($P = 0.001$). The change of Xrs_5 in all three EOT positive groups exceeded 80%. There was no difference between the three groups with regard to the other pulmonary function tests.

Figure 2 shows the relative changes of Xrs_5 (**Figure 2A**) and Rrs_5 (**Figure 2B**) according to the degree of changes in oxygen saturation. The mean baseline SpO_2 was 98.5 ± 0.69% (range 98.4-98.7%). There was a statistically significant difference between Xrs_5 and Rrs_5 among groups ($P < 0.001$). However, Xrs_5 showed a higher correlation with changes in saturation (r = -0.578, $P < 0.001$) than Rrs_5 (r = -0.426, $P < 0.001$). The adjusted R squared of Xrs_5 affecting SpO_2 in regression coefficients was 0.34 ($P < 0.001$), whereas the adjusted R squared of Rrs_5 was 0.18 ($P < 0.298$) (**Table 4**).

Table 3. Results of lung function tests categorized by the last step, grouping EOT⁺

	PCw⁺	PCs⁺	PCr⁺	*P* value
Baseline lung function				
Xrs_5, Z score	-0.77 (-1.10 to -0.59)	-0.76 (-1.13 to -0.58)	-0.45 (-1.68 to -0.20)	0.205
Rrs_5, Z score	-1.54 (-2.29 to -0.02)	-0.90 (-2.93 to -0.54)	-1.63 (-2.48 to 0.33)	0.164
FEV_1, Z score	0.02 (-1.25 to 1.14)	0.00 (-0.23 to 1.37)	0.60 (-0.73 to 2.15)	0.641
FEV_1/FVC	93.0 (84.8 to 95.8)	96.1 (91.8 to 97.3)	93.2 (83.7 to 96.8)	
Xrs_5 last step lung function				
%change	**151.3 (78.2 to 203.8)**	**232.7 (207.0 to 273.7)***	**95.9 (73.4 to 132.4)†**	**0.001**
Z score	-3.23 (-3.67 to -1.87)	**-4.43 (-5.11 to -3.32)**	**-2.70 (-3.66 to -1.14)†**	**0.033**
Rrs_5 last step lung function				
%change	41.9 (24.8 to 70.1)	56.0 (34.8 to 79.6)	30.8 (20.7 to 49.1)	0.189
Z score	-4.37 (-6.30 to -3.19)	-5.27 (-8.51 to -3.29)	-3.48 (-5.89 to -1.29)	0.229
FEV_1 last step lung function				
%change	-32.8 (-44.1 to -21.4)	-46.0 (-48.8 to -31.4)	-30.4 (-53.5 to -26.2)	0.520
Z score	-3.79 (-5.06 to -2.15)	-3.82 (-4.81 to -2.57)	-3.45 (-5.37 to -2.19)	0.986

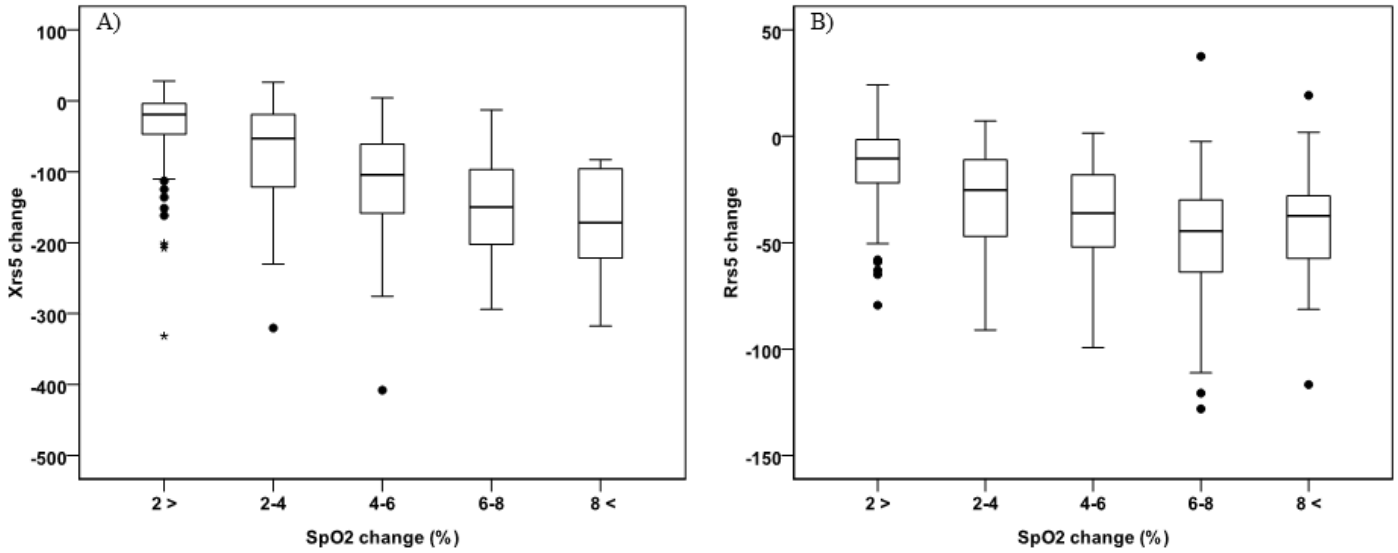

Figure 2. Relative changes in resistance and reactance at 5 Hz with regard to changes in SpO_2. Xrs_5 showed a higher inverse correlation with changes in saturation (r = -0.578, $P < 0.001$) than Rrs_5 (r = -0.426, $P < 0.001$).

Table 4. Multivariate linear regression analysis of risk factors associated with changes in oxygen saturation during methacholine challenge testing (n = 372 tests)

	Adjusted R^2	Coefficient	SE	P value
Change in Xrs_5	0.34	-0.537	0.002	<0.001
Change in Rrs_5	0.18	0.060	0.006	0.298

Changes in IOS parameters before EOT+

Since the parameters of IOS are susceptible to changes before the occurrence of airway obstruction, we assessed percent changes in lung function from baseline to Last-1 and Last-2 steps as well as the last step (**Figure 3**). All parameters demonstrated significant changes when compared with the previous step ($P < 0.001$). Using ROC curves, we determined the relationship between the sensitivity and specificity in the percent change of Xrs_5 and Rrs_5 for predicting of PC_{80}—Xrs_5 and PC_{40}—Rrs_5 (**Figure 4**). The AUC of Xrs_5 (0.837, 95%CI 0.765-0.909) was larger than that for Rrs_5 (0.812, 95%CI 0.744-0.879). A forty-nine percent decrease in Xrs_5 was the optimal point of sensitivity (62.5%) and specificity (90.7%) for predicting a 80% change of Xrs_5 at the following step. The cutoff point of PC_{40}—Rrs_5 was 19.1% with a lower sensitivity and specificity (31.6% and 68.4%, respectively) than those of reactance.

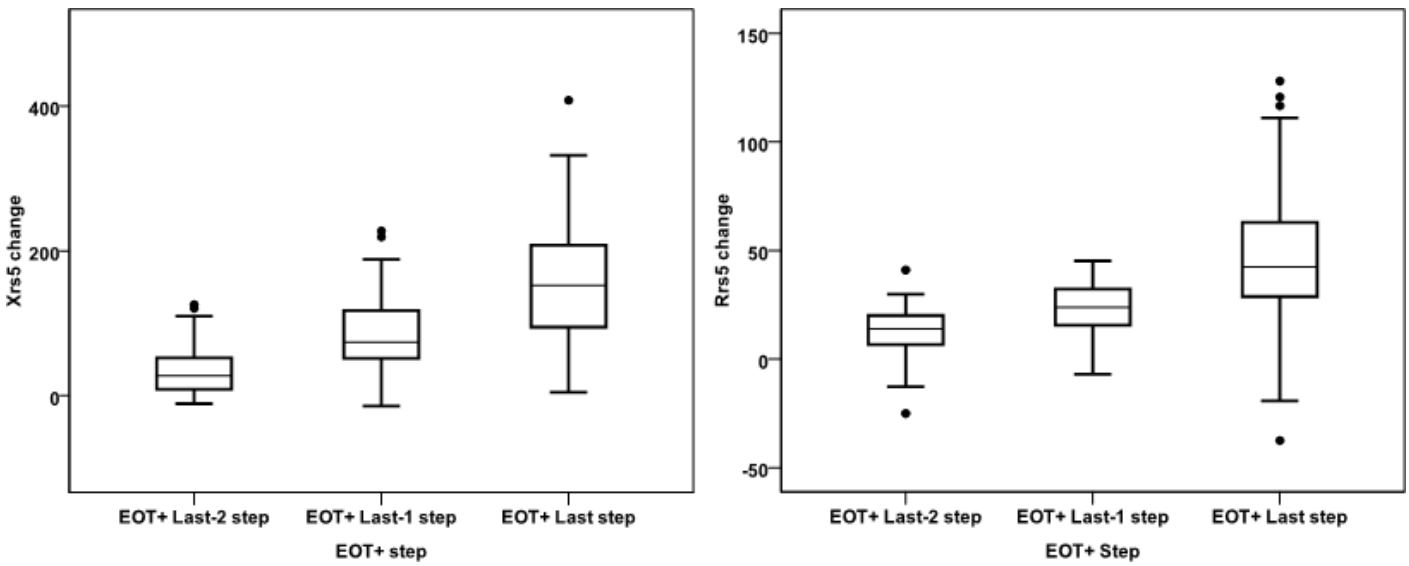

Figure 3. Mean percent changes in reactance and resistance at 5 Hz and 10 Hz at EOT+, one step prior to EOT+ and two steps prior to EOT+ in all subjects. At EOT+, all parameters changed significantly compared to the previous step ($P < 0.001$).

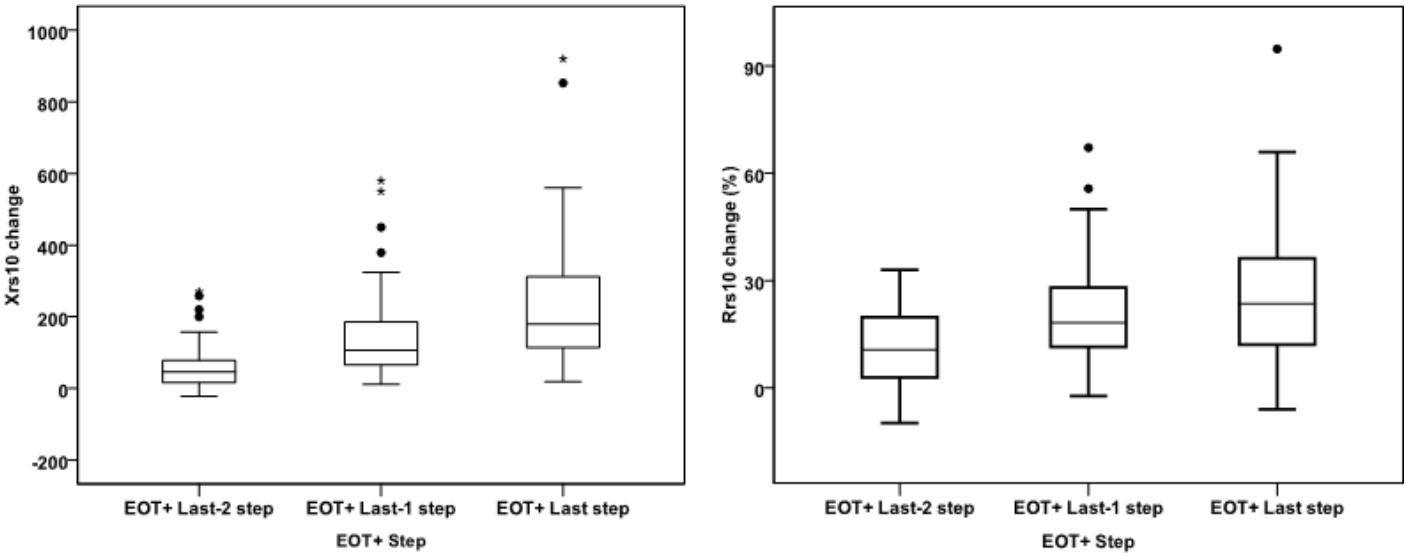

Figure 3. (Continued)

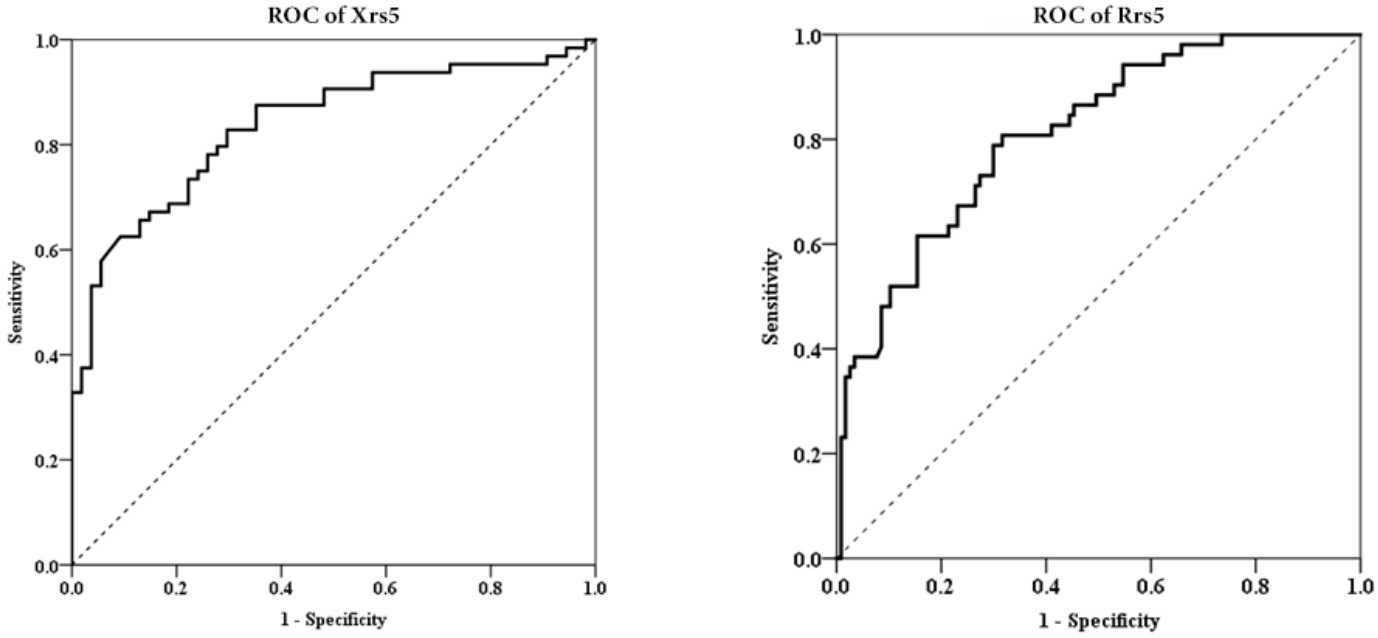

Figure 4. The ROC curves describing the relationship between the sensitivity and specificity in the percent change of Xrs_5 and Rrs_5 for the prediction of PC_{80}–Xrs and PC_{40}. The AUC of Xrs_5 was larger than that of Rrs_5.

Discussion

In this study we measured the relative changes and Z scores of Xrs_5 and Rrs_5 when EOT was reached. We found that percent change of FEV_1 in preschool children was similar to that observed in previous studies with the presence of wheezing.[3,4,27] When the test was stopped due to respiratory symptoms, resistance did not exceed 40% and positive rate of PC_{40}–Rrs_5 was even higher in EOT^- group than that in EOT^+ group. Therefore, a 40% change in Rrs_5 may not be an appropriate parameter in bronchial challenge testing. The percent changes and Z scores of Xrs_5 better represent changes in saturation than percent changes and Z scores of Rrs_5. Although FEV_1 and Xrs_5 reflect different pathophysiologic changes in the lungs, Xrs_5 showed good agreement with the decline in FEV_1.[28] Because it is difficult to process the 10 steps of bronchoprovocation tests with doubling doses in preschool children, we suggest beginning the test by quadrupling doses and switching to doubling doses when 51.4% of Xrs_5 is reached.

In children with EOT^+, they show higher changes than the reference values in most cases.[21,24,25] In addition, pulmonary function test was positive even when EOT was negative in many cases. With regard to resistance, positive rate of PC_{40}–Rrs_5 was even higher in the EOT^- group than that in the EOT^+ group. This suggests that even if the respiratory symptoms are absent, oxygen saturation is normal, or wheezing is not auscultated, the patient may already have bronchoconstriction and thus be in danger of developing respiratory difficulty in some cases. Therefore, these clinical parameters were not able to detect the pulmonary function changes at the early stage, and if these are

used as a standard endpoint for the bronchial challenging test, the diagnosis of asthma may not be made accurately and be at risk sometimes.

Comparing Xrs_5 and Rrs_5 in IOS, the changes of Xrs_5 in all three EOT positive groups exceeded 80% compared to the results reported in previous studies and were lowest in PCr^+, followed by PCw^+ and PCs^+. On the other hand, Rrs_5 did not show greater than a 40% change even when the child had to stop the test due to respiratory symptoms. This suggests that PC_{40}–Rrs_5 may not be a suitable value in preschoolers during challenge test. As a sensitive indicator of airway obstruction, Xrs_5 is more useful than Rrs_5, a finding corresponding well with previous studies.[24] The parameters of IOS and spirometry reflect different properties of the respiratory system.[2] However, changes in IOS parameters are well correlated with those in FEV_1 in many studies.[7,14,23] As shown in our previous studies, we investigated which IOS parameter is more correlated with BHR and found that reactance better reflects BHR than resistance. We do not have clear explanation for this finding. Further research is warranted to describe the significant physiological correlation of reactance with BHR.

Since the respiratory symptoms and wheezing were not comparable with IOS parameters numerically during the examination, we compared the changes in oxygen saturation with parameters and reactance showed a more significant change with the saturation. Consequently, in preschoolers, reactance, rather than resistance, reflects bronchial hyperresponsiveness in methacholine challenge test. As we previously mentioned, the clinical parameters may lead to a dangerous situation in preschooler because most of cases have already exceeded the reference value when the test was completed and we found the reactance was a better parameter for determining the bronchial hyperresponsiveness. Therefore, we determined the optimal reactance value for examining carefully before proceeding the test by comparing the last step with the previous steps, and found that a 49% decrease in Xrs_5 indicated an 80% change in reactance at the following step. Thus, if the reactance decreases to near 49% in preschoolers during the methacholine test, we recommend lowering the concentration at the next step.

The appropriate increases in concentration during methacholine challenge testing have not been determined. Some recent studies reported that preschool children successfully completed methacholine challenge testing when concentrations were tripled.[29,30] However, these studies are limited in that they included a small number of subjects and that the initial start-up concentration was relatively high, and the test time was short. In contrast, our study using methacholine in four fold increments had a lower success rate of spirometry, but the IOS success rate was even higher up to 98%. Therefore, we suggest that in the case of young preschoolers, the methacholine test using spirometry can be performed by raising the starting concentration and increasing the concentration by three or four times. It may also be useful to perform methacholine test using IOS due to the notion that IOS requires minimal patient cooperation. The risk of severe bronchoconstriction can be minimized by lowering the concentration when a certain change is observed in previous results. However, further research is needed to determine changes in lung function when apply doubling doses. Another limitation was the difficulty of defining EOT^- due to lack of a healthy control group.

In the methacholine challenge test using IOS, which can be done more easily in preschooler than spirometry, reactance better reflects bronchial hyperresponsiveness than resistance. Therefore, we suggest switching to doubling doses when reactance reaches a certain level in order to minimize the risk of severe bronchoconstriction and increase the success rate.

Acknowledgements

No author has a financial conflict of interest with regard to the material presented in this paper.

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