

Utility of impulse oscillometry in young children with asthma

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Impulse Oscillometry (IOS) was developed as a tool to measure lung function, and as it only requires passive cooperation, it has been successfully used in younger children. The aim of this study was to assess the utility of IOS compared to conventional spirometry for lung function measures in asthmatic Korean children aged 3 to 6 yrs. Total serum IgE levels, total eosinophil counts, and specific IgE levels were measured in 77 children with asthma and 55 control subjects. IOS and spirometry were performed in the children before and after bronchodilator administration. Asthmatic children significantly differed from control subjects in baseline resistance at 10 Hz and in their IOS-assessed bronchodilator responses through a Δ resistance at 5 Hz (mean, -27.4% vs. -13.1% ; $p = 0.002$), 10 Hz (mean, -20.4% vs. -11.5% ; $p = 0.012$), 20 Hz (mean, -16.4% vs. -9.4% ; $p = 0.016$), and 35 Hz (mean, -17.2% vs. -10.2% ; $p = 0.020$). Conventional spirometry did not show statistically significant findings. Asthmatic children significantly differed from control subjects in IOS-assessed bronchodilator response through a Δ resistance at 5 Hz, both in atopic children and in non-atopic children. For atopic children, atopic asthmatic children ($n = 58$) also significantly differed from atopic controls ($n = 30$) in baseline resistance at 10 Hz, 20 Hz, 35 Hz and impedance and in IOS-assessed bronchodilator responses through a Δ resistance at 10 Hz and 35 Hz. There were some significant correlations between bronchodilator responses of spirometric parameters and IOS parameters. IOS is useful diagnostic tool in early asthma development and might be a helpful objective outcome measure of early interventions.

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Asthma is considered one of the most common chronic diseases in childhood (1). Because asthma usually starts in the early stages of life (2), early intervention has become a focus of recent research in the hope that appropriate measures will affect the natural course of the disease. The benefits of early anti-inflammatory treatment in asthma have been widely reported (1, 3, 4). Assessment of the resistive properties of the respiratory system in young children has not been easy. The most frequently used measurement of low airway obstruction in older children is the forced expiratory volume in 1 s (FEV₁)

obtained from a maximal expiratory flow volume curve through conventional spirometry. However, the requirement of forced expiratory maneuvers makes evaluation difficult, especially in young children. During infancy, several lung function tests can be performed, but most of these are limited to the first 2 yrs of life and can only be performed in research laboratories because of the highly technical requirements (5).

In 1993, a modification of the forced oscillation technique (FOT), impulse oscillometry (IOS) was introduced by Jaeger as a user-friendly, commercialized apparatus offering measure-

ments of respiratory system resistance (R) and reactance (X) at number of frequencies (6). IOS requires little cooperation from the patients as only tidal volume breaths are required, and therefore children up to 2 yrs old can easily be examined (7). So, IOS was evaluated as a new technique for the assessment of airflow obstruction in young children (6). Resistance parameters are measures during spontaneous quiet breathing. They may therefore be more representative of normal breathing in daily life situations rather than forced expiratory maneuvers. The approach of IOS differs from the original FOT idea, wherein a rectangular pressure impulse is applied rather than a pseudorandom pressure wave (being the sum of several sinusoidal pressure waves), but IOS offers the same advantages. It requires little cooperation from the patients, and it is a rapid, easy, and a reproducible measurement of airflow obstruction. There are only a limited number of studies using IOS. It is also well recognized that race frequently influences the relationship between this determinant and the lung function parameter (8). To our knowledge, there are no published studies on the use of IOS in Asian children.

The aim of this study was to assess the utility of IOS for lung function measure in asthmatic Korean children, aged 3 to 6 yrs compared with conventional spirometry. We further analyzed baseline values and post-bronchodilator responses of IOS in atopic asthma, atopic control, non-atopic asthma, and non-atopic control groups.

Materials and methods

Subjects

We evaluated 77 children with asthma and 55 control subjects, aged 3 to 6 yrs, who visited allergy clinic for asthma or a general health work-up at the Severance Hospital of Yonsei University. All patients with asthma were physician-diagnosed and gave positive responses to at least 4 of 5 questions of a modified American Thoracic Society (ATS) symptom questionnaire reflecting respiratory symptoms (wheeze with colds, wheeze apart from colds, dyspnea associated with wheeze, wheeze after exercise, persistent cough) during the 12 months preceding the visit. The control children were recruited from subjects who had received a general health work-up. They did not have any history of allergic or inflammatory disease. All subjects were drug-free for the duration of the study. Baseline FEV₁ of all subjects were over 70% of predicted. Children

were not allowed to use bronchodilators at least 24 h prior to the test. At the initiation of the study, total serum IgE levels and peripheral blood eosinophil counts were routinely determined. Total and specific IgE levels were measured by using the Pharmacia CAP assay (Uppsala, Sweden). A specific IgE test was performed with six common allergens in Korea, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, egg whites, cow milk, German cockroach and *Alternaria*. According to the manufacturer's instructions, specific IgE levels of over 0.35 KU_A/l were considered positive. Atopic children were defined as those who were sensitive to more than one of six common allergens and their total IgE levels were more than 100 IU/ml. The Severance Hospital Institutional Review Board approved this study, and informed consent was obtained from the parents of the children.

Impulse oscillometry

A Jaeger MasterScreen IOS system (Jaeger Co, Wurzburg, Germany) was used. The system was calibrated through a single volume of air (3 l) at different rates (flow) and also with a reference resistance device (0.2 kPa/l/s) per manufacturer. The machine was also calibrated for body temperature and pressure of saturated gas. An impulse generator produced brief pressure pulses at intervals of 0.2 s. The spectral ratio of the amplitude of the pressure wave signal to the resulting flow signal constituted the impedance of the total respiratory system from which the total R and X of the respiratory system were calculated (9, 10). In this study, mean R and X values were calculated over a measurement period of 60 s in the frequency range of 5–35 Hz.

During IOS measurement, the children were sitting upright with their heads resting against the back of the chair. The children used nose clips. They were instructed to breathe quietly through a mouthpiece. To decrease the shunt compliance of the cheeks, the investigator stood behind the patient and supported both the cheeks and the chin with their hands. The observations did not have artifacts caused by coughing, breath holding, swallowing, or vocalization. Three correct measurements were averaged at each time point.

Spirometry

Forced expiratory volume, forced vital capacity (FVC), forced expiratory flow between 25% and 75% of expired vital capacity (FEF_{25–75%}) and

maximum mid-expiratory flow (MMEF) were measured with a computerized spirometer (Vmax22; Sensormedics, CA, USA) and calibrated according to age, sex, height, weight, and race (11) and are expressed in percent predicted. Because young children are rarely able to meet strict ATS criteria for spirometry, modified criteria were used based on the findings of Aret et al. (12) and Eigen et al. (13). These criteria consisted of visually reproducible shapes of flow-volume curves, forced expiratory time of greater than 1 s, consistent peak expiratory flows, and FEV₁ and FVC values within 0.2 l of each. Temperature and atmospheric pressure were measured during the pulmonary function test, and a leak test was taken before the pulmonary function test. Quality control was performed with a 3-l syringe calibration. The children were coached through standard forced expiratory maneuvers. The best of three technically acceptable blows were recorded and the best values were retained. Spirometry was not performed in ten children and were excluded from the analysis.

Study protocol

Impulse oscillometry measurements were performed immediately before spirometry measurements to prevent an unfavorable effect of deep inhalation on the IOS parameters. After a baseline IOS and spirometry measurement, a salbutamol (two puffs, 200 µg) metered-dose inhaler was administered via a spacer device

(Volumatic, Glaxo Wellcome, Burgos, Spain). Fifteen minutes after administration of salbutamol, all tests were performed in the same sequence as the baseline test.

Statistical analysis

Results were expressed as mean with 95% CI. Data were analyzed with *t*-tests and Pearson's correlation tests. The receiver operating characteristic (ROC) curves plot all possible combinations between the true positive ratio (sensitivity; *y*-axis) and the false positive ratio (1-specificity; *x*-axis) as one varies the definition of positivity. *P*-values less than 0.05 were considered statistically significant.

Results

Lung function measures with IOS were well tolerated by all the subjects. There were no significant differences in age, sex, height or weight between the asthmatic and the control group. In the asthmatic group, 75% showed evidence of atopy and in the control group 55% showed evidence of atopy (Table 1). Mean with 95% CI level of specific IgE for atopic children was 22.8 (12.2 to 33.4) KU_A/l. All atopic children in our study were sensitive to more than two allergens.

Before bronchodilator administration, there was a significant difference at R10 (R at 10 Hz) between the asthmatic group and the control

Table 1. Impulse oscillometry measurements in 3- to 6-year-old children with and without asthma

Parameter	Asthma (n = 77)	Control (n = 55)	p-value
Age (yrs)	4.9 (4.7 to 5.1)	5.1 (4.9 to 5.3)	0.157
Sex (male/female)	48/29	35/20	0.880
Height (cm)	112.5 (111.0 to 114.1)	113.0 (111.2 to 114.7)	0.689
Weight (kg)	21.2 (20.0 to 22.3)	20.1 (20.0 to 21.9)	0.172
Atopy (%)	75	55	
Before bronchodilator			
Resistance at 5 Hz (hPa/l/s)	0.95 (0.86 to 1.04)	0.88 (0.80 to 0.97)	0.301
Resistance at 10 Hz (hPa/l/s)	0.80 (0.74 to 0.86)	0.70 (0.64 to 0.77)	0.035
Resistance at 20 Hz (hPa/l/s)	0.57 (0.53 to 0.62)	0.52 (0.46 to 0.56)	0.079
Resistance at 35 Hz (hPa/l/s)	0.70 (0.66 to 0.75)	0.65 (0.60 to 0.70)	0.101
Reactance at 5 Hz (hPa/l/s)	-0.28 (-0.38 to -0.19)	-0.29 (-0.39 to -0.21)	0.823
Impedance (hPa/l/s)	1.05 (0.93 to 1.17)	0.94 (0.79 to 1.09)	0.267
Resonant frequency (hPa/l/s)	17.78 (15.68 to 19.9)	16.69 (14.17 to 19.21)	0.506
Bronchodilator response			
ΔResistance at 5 Hz (%)	-27.4 (-21.0 to -33.7)	-13.1 (-7.8 to -18.4)	0.002
ΔResistance at 10 Hz (%)	-20.4 (-15.1 to -25.7)	-11.5 (-8.4 to -14.5)	0.012
ΔResistance at 20 Hz (%)	-16.4 (-12.2 to -20.6)	-9.4 (-6.0 to -12.7)	0.016
ΔResistance at 35 Hz (%)	-17.2 (-12.9 to -21.6)	-10.2 (-7.0 to -13.4)	0.020
ΔReactance at 5 Hz (%)	-22.9 (-93.9 to 48.2)	40.7 (-91.8 to 173)	0.399
ΔImpedance (hPa/l/s)	-12.0 (-31.5 to 7.7)	18.2 (-22.1 to 58.5)	0.178
ΔResonant frequency (hPa/l/s)	20.8 (-3.5 to 45.0)	-7.7 (-30.8 to 15.4)	0.089

Results are indicated as mean with 95% CI.

group (Table 1). We evaluated the bronchodilator response to salbutamol and compared the results obtained with IOS and spirometry. After bronchodilator use, asthmatic children significantly differed with control subjects in their IOS-assessed bronchodilator responses through percentage change of R5, R10, R20 and R35 (Table 1). By contrast, conventional spirometry values did not show statistically significant differences between asthmatic children and control subjects at baseline or in the bronchodilator response (data not shown). ROC curve for describing relationship between sensitivity and specificity of changes in IOS-assessed bronchodilator responses of R5 and R10 to detect clinical asthma also were shown. The area under the ROC curve were 0.663 (R5, $p = 0.002$) and 0.609 (R10, $p = 0.040$), respectively (Fig. 1).

We further compared children according to asthma and atopic sensitization. We divided the subjects into atopic asthmatic, atopic control, non-atopic asthmatic, and non-atopic control groups. There were no significant differences in age, sex, height or weight among the groups. For atopic children, atopic asthmatic children ($n = 58$) vs. atopic controls ($n = 30$) significantly differed in R10, R20, R35 and impedance at baseline (mean, 0.81 hPa/I/s, 0.58 hPa/I/s, 0.71 hPa/I/s, 1.02 hPa/I/s vs. 0.65 hPa/I/s, 0.48 hPa/I/s, 0.62 hPa/I/s, 0.78 hPa/I/s, respectively). After bronchodilator use, atopic asth-

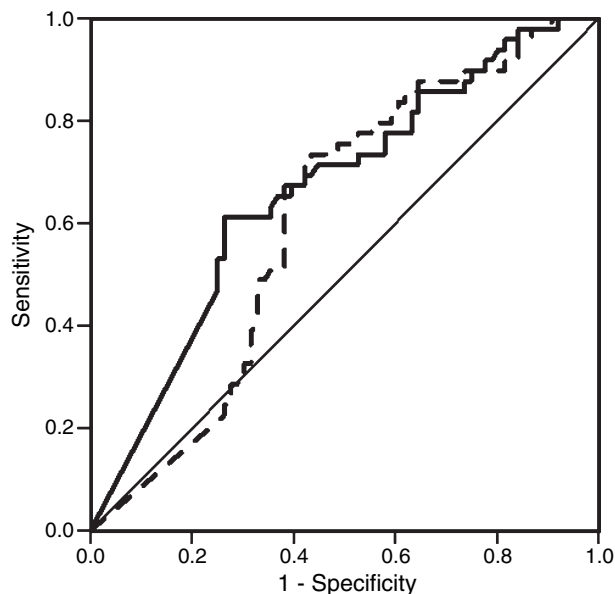


Fig. 1. Receiver operating characteristic curve describing relationship between sensitivity and specificity of changes in impulse oscillometry-assessed bronchodilator responses of resistance at 5 Hz (line) and 10 Hz (dot) to detect clinical asthma.

matic children vs. atopic controls significantly differed in the percent change of R5, R10 and R35 (mean, -27.0% , -21.3% , -18.8% vs. -14.7% , -12.6% , -10.6% , respectively). But, conventional spirometry values did not show statistically significant differences between atopic asthmatic children and atopic control subjects at baseline or in the bronchodilator response (data not shown). Between nonatopic asthmatic children ($n = 19$) and nonatopic controls ($n = 25$), bronchodilator response of R5 also showed significant differences (mean, -28.4% vs. -10.7%). Conventional spirometry values both of baseline and of bronchodilator response showed no significant differences between non-atopic asthmatic and nonatopic control subjects (data not shown). ROC curve for describing relationship between sensitivity and specificity of changes in IOS-assessed bronchodilator responses of R5 to detect clinical asthma also showed significant findings both in atopic children and in non-atopic children. The area under the ROC curve were 0.625 ($p = 0.04$) and 0.736 ($p = 0.012$), respectively. Individual values of bronchodilator response of R5 also were shown in Fig. 2. There were some significant correlations between bronchodilator responses of spirometric parameters (FEV_1 , FVC and peak expiratory flow) and IOS parameters (R10, R20 and R35) (Table 2).

Discussion

To our knowledge, this is the first study to investigate the relationship of IOS with a clinical asthma in young Asian children. We have shown that asthmatic young children vs. control

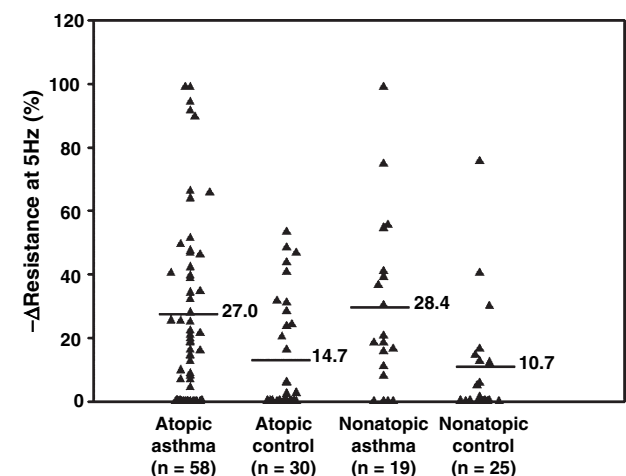


Fig. 2. Impulse oscillometry-assessed bronchodilator responses of resistance at 5 Hz. Percentage change in response to salbutamol is represented as individual values (black dots) and means (number with horizontal lines).

Table 2. Pearson correlation coefficients between bronchodilator responses of spirometric parameters and of IOS parameters in 3- to 6-year-old children

		$\Delta R5$	$\Delta R10$	$\Delta R20$	$\Delta R35$
ΔFEV_1	r	0.143	0.518	0.508	0.446
	p	0.308	<0.001	<0.001	0.001
ΔFVC	r	0.055	0.478	0.510	0.381
	p	0.695	<0.001	<0.001	0.005
ΔPEF	r	0.222	0.483	0.461	0.444
	p	0.113	<0.001	0.001	0.001

IOS, Impulse oscillometry; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow.

subjects significantly differed in baseline R10 and in IOS-assessed bronchodilator responses through percentage change in R5, R10, R20 and R35. We aimed to compare the usefulness of IOS with that of conventional spirometry in lung function measure between healthy and asthmatic young children. We also compared the baseline value and bronchodilator response of IOS relative to asthma and atopic sensitization and showed that asthmatic children significantly differed from control subjects in bronchodilator response of R5 both in atopic children and in non-atopic children.

Assessment of the resistive properties of the respiratory system in children is not easy. However, other studies have shown that IOS is well accepted by children above 4 yrs (14, 15). The success rate of IOS in both healthy (16, 17) and mixed population of asthmatic and healthy young children was greater than 83% (8). Some investigators have even revealed that children up to 2 yrs old can be examined (7). In the present study, IOS was also well accepted by all subjects (aged 3–6 yrs).

Previous studies in children have shown a correlation between IOS measurements and other measurements of lung function (7, 18, 19). FEV₁ and R values are likely to reflect different pathophysiological aspects of airflow obstruction. FEV₁ is measured during the maximal expiration from the maximal inspiratory lung volume, while R values are measured during tidal breathing. Changes in FEV₁ values are largely caused by changes in airflow limitation, while R values are more directly related to airway caliber. Olaguibel et al. showed IOS parameters R5 and R20 correlated with FEV₁ at both baseline and post-bronchodilator in 38 asthmatic children aged 3 to 6 yrs (14). In spite of the fact that conventional forced breathing tests are considered the 'gold standard' for measuring airflow obstruction, reliable spirometry is difficult to perform in young children. Only one previous study has compared IOS and spirome-

try for diagnosing asthma in young children. Marotta et al. (15) showed that IOS was better than spirometry in discriminating between 4-year-old asthma-prone children with or without asthma on the basis of their bronchodilator response and they showed significant different finding for asthmatic children only in atopic subgroups. They have shown no significant differences in baseline IOS parameters between the asthmatic and non-asthmatic children and in bronchodilator response of IOS parameters between the asthma and non-asthma in non-atopic subgroups (15). However, in our study, baseline R10 was also significantly different between asthmatic children and control subjects. And we showed that asthmatic children significantly differed from control subjects in bronchodilator response of R5 both in atopic and non-atopic children. Differences in characteristics and race of subjects may explain discrepancies between our study and Marotta's study. In Marotta's study, non-asthmatic subjects also had three or more episodes of wheezing in early life despite a lack of clinical symptoms for the preceding 12 months (15). In contrast to Marotta's study, we compared clinically asthmatic children with healthy children as a control.

Several studies have tried to determine how much R changes after the administration of B₂-agonists in healthy children vs asthmatics to identify the cut-off level that can be used in the diagnosis of asthma. Previous studies have suggested that asthma can be reliably diagnosed with the following IOS bronchodilator response values: a 20% to 40% decrease in R5 (8, 15, 20) and a 15% to 30% decrease in R10 (15, 21). Even in healthy children, inhalation of a bronchodilator reduces the values of R5 (8, 20) suggesting that IOS can detect minimal changes in airway caliber (17). In the present study, we suggest 20% of decrease in R5 after bronchodilator administration in children with a mean age of 4.9 yrs as positive bronchodilator response on the basis of a 95% CI of non-asthmatic control subjects (−7.8 to −18.4%). The risk of overinterpretation of a change after bronchodilation should be considered, but the present values with 95% CI can be an important tool against overinterpretation.

We further compared children according to asthma and atopic sensitization. We divided the subjects into atopic asthmatic, atopic control, non-atopic asthmatic, and non-atopic control groups. R5 and X5 have repeatedly been shown to exhibit a significantly negative and positive correlation, respectively, between age, height and weight (8, 16, 17). In this study, there were no significant differences in age, sex, height or weight

among groups. Atopy is a risk factor for persistent asthma (22). Marotta et al. (15) showed that IOS is especially useful in the subgroup of atopic children. In our study, we also revealed that more significant findings of baseline and bronchodilator response of IOS for asthmatic children were in atopic subjects than in non-atopic subjects. However, both in atopic children and in non-atopic children, asthmatic children significantly differed from control subjects in bronchodilator response of R5. So, we could suggest that bronchodilator response of R5 is the best IOS parameter for detecting asthma in both young atopic children and nonatopic children.

Although there were no significant changes in conventional spirometry, we could find some significant correlations between bronchodilator responses of spirometric and IOS parameters. These findings also supported the results of IOS as reasonable.

In conclusion, we have shown that IOS values are superior to spirometry values in assessment of clinical asthma of young children on the basis of their bronchodilator response. IOS provided an objective lung function measurement that correlated with the clinical definition of asthma in young children. Therefore, we suggest that IOS may be a potentially helpful outcome measurement for early intervention.

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