

Evaluation of Impulse Oscillometry During Bronchial Challenge Testing in Children

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Summary. Background: The impulse oscillation system (IOS) allows easy measurement of respiratory system impedance (Zrs). The aim of this retrospective study was to evaluate the accuracy of IOS parameters obtained during methacholine challenge by comparison with “the gold standard” forced expiratory volume in the first second (FEV₁). Methods: Measurements of FEV₁ and resistances at 5 and 20 Hz, reactance at 5 Hz, impedance at 5 Hz and resonant frequency were performed in 227 children with suspected asthma, before and during methacholine challenge. Data were analyzed in the overall population and in three subgroups according to the final diagnosis: asthma (n = 72), chronic cough and nonspecific respiratory symptoms (n = 122), allergic rhinitis (n = 33). Results: All IOS parameters changed significantly during the tests but only changes in X5 were significantly different between responders and nonresponders. Moreover, changes in IOS parameters were not correlated with changes in FEV₁, apart from a weak correlation for X5. The receiver operating characteristic (ROC) curve for changes in X5 (to predict a 20% decrease in FEV₁) showed a best decision level for a 50% decrease in X5 with a sensitivity of 36% and a specificity of 85%. Results were not different in the asthma group. Conclusion: The accuracy of measurements by IOS during methacholine bronchial challenge in children was not suitable when compared with FEV₁. It could be assumed that spirometry and IOS, while both providing indirect indices of airway patency, are exploring different mechanisms, each with its own methodological potentials and limitations. **Pediatr Pulmonol.** © 2011 Wiley-Liss, Inc.

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INTRODUCTION

Bronchial hyperreactivity is a key feature of asthma. Its detection during a nonspecific bronchial challenge test is an important contribution to the diagnosis in children, where the clinical presentation may be atypical. A decrease of 20% or more from the baseline forced expiratory volume in the first second (FEV₁) value is usually used to define a positive test.¹ However, forced expiratory maneuvers are usually difficult in young children because they require active cooperation from the patient. Impulse oscillometry (IOS) is an alternative technique for studying respiratory system properties. This method has several advantages: it does not require active cooperation, is noninvasive, rapid and easy to perform. IOS has been introduced as a user-friendly, commercial version of the classical forced oscillation technique (FOT). FOT has been proven to be valuable for measuring baseline lung function² and for assessing changes in bronchomotor tone during bronchodilation² and bronchoprovocation tests.^{3,4} Conversely, only a limited number of studies have been carried out using IOS. The IOS is, however, different from the classical FOT and if these two techniques are in principle comparable, they are not identical.⁵ To our knowledge, all

the studies using IOS during nonspecific bronchial challenge in children have been conducted with small numbers of patients, all asthmatic and under laboratory conditions. The aim of the present study was to assess the accuracy of measurements by means of IOS during methacholine challenge in a large non-selected population of children with suspected asthma, in routine practice. In order to compare the method with conventional forced breathing tests as the “gold standard” for

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airflow obstruction, the study was performed in children who were able to perform the FEV₁.

PATIENTS AND METHODS

Patients

This retrospective study included 227 children (127 boys and 100 girls) who had been referred by their physicians to the laboratory for evaluation of bronchial responsiveness. The study population was pooled into three subgroups according to the final diagnosis: asthma ($n = 72$), chronic cough and other nonspecific respiratory symptoms ($n = 122$), allergic rhinitis ($n = 33$). Fifty patients (22%) were less than seven years old and seven patients (3%) were greater than fifteen years old. All children had a baseline FEV₁ of greater than 80% of predicted values. The patients were free of recent viral infection and they discontinued their β_2 -agonist medications for at least 12 hours before the challenge. The study was approved by the local ethics committee.

Measurements of Forced Expiratory Flows

Maximal expiratory flow volume (MEFV) measurement was performed using a spirometer (Autospiro PAL, Minato Medical, Japan). The best MEFV curve according to ATS criteria, from at least three attempts, was used.⁶ The baseline ratio FEV₁/FVC was calculated.

Measurements of Respiratory Impedance

The basic principle of IOS and other forced oscillation techniques has been described elsewhere.⁷ In this study, measurements were made using commercially available equipment (Master Screen; E. Jaeger, Germany). They were carried out during stable, tidal breathing through a Y-mouthpiece. Children were comfortably seated with their head in a neutral position, their nose clipped, their cheeks and chin supported with hands to avoid the "upper airway shunt" and their lips firmly closed around the mouthpiece. During data acquisition, pressure, and flow traces were graphically displayed in real time. Measurements were accepted when the tracings showed uninterrupted breathing during acquisition, over a 30-sec interval of time. The parameters yielded were: resistance at 5 Hz (R5), resistance at 20 Hz (R20), reactance at 5 Hz (X5), impedance at 5 Hz (Z5), expressed in hPa s L⁻¹ and the resonant frequency (f0) expressed in Hz.

Protocol

Baseline IOS measurements were performed before FEV₁. Methacholine aerosols were generated by a nebulizer-dosimeter (Mediprom FDC) with a mouthpiece.

The initial methacholine dose was 25 μ g, followed by administration in doubling doses up to a maximal cumulative quantity of 1,500 μ g, or until a positive response was indicated by a decrease in FEV₁ $\geq$ 20% (PD₂₀). IOS measurement was performed as soon as the FEV₁ had decreased by 20% or more, or after the maximal dose had been administered.

Data Analysis

Comparisons between subgroups of children for their anthropometric and baseline spirometric data were performed using an analysis of variance (ANOVA). For comparison of paired data, paired Student's *t*-tests were used. For comparison of changes in IOS parameters between responders and nonresponders, Student's *t*-tests (for independent samples) were calculated. To study the relationship between FEV₁ and IOS parameters in the overall population, Pearson's correlation coefficients (*r*) were used. In each subgroup, this analysis was performed using the Spearman's rank correlation coefficient (ρ) (non-normal sampling distribution). Contingency tables describing the number of subjects correctly classified as positive or negative for bronchial hyperresponsiveness by a 50% increase in R5 and a 50% decrease in X5⁷ versus the "gold standard" 20% decrease in FEV₁ were performed and Chi2 values were calculated. To describe the sensitivity and specificity of changes in IOS parameters in response to bronchial challenge in comparison to changes in FEV₁, receiver operating characteristic (ROC) curves were constructed. The area under the ROC curves was a measure for the overall discriminatory performance of a test. Statistical significance was considered at *P* values < 0.05 .

RESULTS

Of the 227 children, 188 had a positive test and 39 were nonresponders.

The anthropometric characteristics and baseline spirometry of the overall population studied and of each subgroup are presented in Table 1. The analysis did not show any subgroup-related difference for age, weight, height, baseline FEV₁, and baseline FEV₁/FVC.

Analysis in the Overall Population

At baseline, all IOS parameters correlated with FEV₁ ($P < 0.0001$, Table 2).

In response to methacholine, the decrease in FEV₁ was associated with an increase in R5, R20, f0, Z5, and a decrease in X5. All differences were statistically significant, not only in responders ($P < 0.0001$) but also in nonresponders ($P < 0.0001$). Among IOS parameters, X5 alone presented a magnitude of change

TABLE 1—Anthropometric Characteristics and Baseline Spirometry of the Study Population*

	Age (years)	Weight (kg)	Height (cm)	FEV ₁ (% pred)	FEV ₁ /FVC (%)
Overall population (n = 227)	9 ± 3.1	34.4 ± 14.9	135.7 ± 18.3	110 ± 22	92 ± 5
Asthma (n = 72)	9 ± 2.9	34.4 ± 16.1	135.2 ± 17.9	109 ± 14	91 ± 5
Chronic cough (n = 122)	8.9 ± 3.1	33.7 ± 14.4	134.8 ± 17.9	115 ± 24	92 ± 5
Allergic rhinitis (n = 33)	9.8 ± 3.5	37.5 ± 14.4	141 ± 19.9	105 ± 18	91 ± 6

*Mean ± SEM.

that was significantly greater in responders than in non-responders ($P < 0.0001$). Correlations between methacholine-induced changes in the “gold standard” FEV₁ and IOS parameters, expressed as percentage change, are shown in Table 3. The changes in FEV₁ did not correlate significantly with those in IOS parameters, except for X5, although this correlation was weak ($r = -0.25$, $P = 0.0001$).

Contingency tables describing the numbers of subjects correctly classified as positive or negative for bronchial hyperresponsiveness by a 50% increase in R5 and a 50% decrease in X5 versus the “gold standard” 20% decrease in FEV₁ are given in Table 4; Chi2 values were, respectively, 0.1 and 5.4 ($P = 0.9$ and $P = 0.02$). Sensitivity and specificity were calculated for R5 (sensitivity = 15%, specificity = 87%) and X5 (sensitivity = 36%, specificity = 85%).

The areas under the ROC curves for methacholine-induced changes in each IOS parameter expressed as percentage, are shown in Table 5. Only that of X5 reached a statistical significance (AUC = 0.61, $P = 0.014$). The ROC curve of the sensitivity and specificity of changes in X5 as a measure to detect a 20% fall in FEV₁ is shown in Figure 1. The point of the X5 ROC curve closest to the upper left-hand corner corresponds to a decrease of 50%, with a sensitivity of 36% and a specificity of 85%.

Subgroup Analysis

The analyses focused on each subgroup, at baseline and after challenge, are presented in Tables 2 and 3. In

the asthma group, as in the overall population, the changes in FEV₁ did not correlate significantly with those in IOS parameters, except for X5 ($\rho = 0.34$, $P = 0.004$). In the chronic cough and other nonspecific respiratory symptoms group, a weak correlation was also observed with the changes in R5 ($\rho = -0.19$, $P = 0.03$) and Z5 ($\rho = -0.23$, $P = 0.01$). Conversely, in the allergic rhinitis group, no correlation was observed between changes in response to methacholine.

Contingency tables describing the numbers of children in each subgroup who were correctly classified as positive or negative for bronchial hyperresponsiveness by a 50% increase in R5 and a 50% decrease in X5 versus the “gold standard” 20% decrease in FEV₁ were constructed. Chi2 values were low and not significant for R5 in each subgroup. In the asthmatic and allergic rhinitis groups, Chi2 values for X5 were, respectively, 3.3 ($P = 0.07$) and 16 ($P < 0.0001$) (not significant in the chronic cough group). Sensitivity and specificity were calculated for X5 in these subgroups: sensitivity = 41%, specificity = 87% and sensitivity = 45% and specificity = 100%, respectively.

DISCUSSION

To the best of our knowledge, no study of IOS accuracy during methacholine challenge has been conducted in such a large population of children with suspected asthma. In this study, only X5 appeared to be sufficiently discriminative for the detection of bronchial hyperreactivity during methacholine challenge. These findings are not in accordance with those of Vink et al.⁸

TABLE 2—Correlations Between FEV₁ and IOS Parameters (Expressed as Percentages) at Baseline Calculated by Pearson's Correlation Coefficient (r) in the Overall Population and by Spearman's Rank Correlation Coefficient (ρ) in Each Subgroup

	R5	R20	X5	f0	Z5
Overall population (n = 227)	$r = -0.73^{\dagger}$	$r = -0.63^{\dagger}$	$r = 0.7^{\dagger}$	$r = -0.63^{\dagger}$	$r = -0.75^{\dagger}$
Asthma (n = 72)	$\rho = -0.41^{\ddagger}$	$\rho = -0.4^{\ddagger}$	$\rho = 0.44^{\ddagger}$	$\rho = -0.26^*$	$\rho = -0.43^{\ddagger}$
Chronic cough (n = 122)	$\rho = -0.61^{\dagger}$	$\rho = -0.52^{\dagger}$	$\rho = 0.6^{\dagger}$	$\rho = -0.52^{\dagger}$	$\rho = -0.63^{\dagger}$
Allergic rhinitis (n = 33)	$\rho = -0.61^{\ddagger}$	$\rho = -0.54^*$	$\rho = 0.57^*$	$\rho = -0.44^*$	$\rho = -0.63^{\ddagger}$

[†]P value FEV₁ versus IOS parameters <0.0001.[‡]P value FEV₁ versus IOS parameters <0.001.*P value FEV₁ versus IOS parameters <0.05.

TABLE 3—Correlations Between Methacholine-Induced Changes in FEV₁ and IOS Parameters (Expressed as Percentage Change From Baseline Level) Calculated by Pearson's Correlation Coefficient (r) in the Overall Population and by Spearman's Rank Correlation Coefficient (ρ) in Each Subgroup

	R5	R20	X5	f0	Z5
Overall population (n = 227)	r = -0.1	r = 0.02	r = -0.25 [†]	r = -0.04	r = -0.15
Asthma (n = 72)	ρ = -0.09	ρ = -0.03	ρ = -0.34*	ρ = -0.02	ρ = -0.15
Chronic cough (n = 122)	ρ = -0.19*	ρ = 0.01	ρ = -0.23*	ρ = -0.05	ρ = -0.23*
Allergic rhinitis (n = 33)	ρ = 0.11	ρ = 0.2	ρ = -0.14	ρ = -0.06	ρ = 0.08

[†]P value FEV₁ versus IOS parameters <0.0001.

*P value FEV₁ versus IOS parameters <0.05.

who reported that values of R5 and R10 correlated with FEV₁, as did values of X5 and X10. However, our findings are not contradictory to those of Bisgaard and Klug.^{9,10} Indeed, if these authors showed that Zrs measurements exhibited convincing covariation with FEV₁, they did not analyze a direct correlation between these parameters. Moreover, our data accord with: (i) those of Bouaziz et al.¹¹ who found no correlation between changes in FEV₁ and those in X6 and R6, and a weak correlation with the changes in X12 and R12; (ii) those of Mansur et al.¹² who observed no significant correlation between R5 and spirometry measurements, whereas X5 showed a weak but statistically significant correlation with FEV₁. We assumed that to have included in our study children with a suspected (but not proved) diagnosis of asthma could be considered as a population bias. However, this population corresponded to the one which was referred to our laboratory in clinical practice for methacholine challenge testing. The analysis restricted to the asthma subgroup did not indicate different results in comparison with the overall population.

In the present study, non-agreement between changes in FEV₁ and IOS values are likely to reflect different pathophysiological aspects of airflow obstruction. The measurement of Rrs includes both upper and lower airway resistance. In our study, changes in R5 and R20 were significant in responders to methacholine but also in nonresponders. This could be partly explained by an increase in upper airway resistance in nonresponders during testing. It is known that laryngeal constriction

may be associated with pharmacologically induced bronchoconstriction in asthmatics¹³ as well as in normal subjects.¹⁴ On the other hand, (i) the glottic aperture has been shown to widen during a forced expiration, probably in relation with the expiratory effort,¹⁵ so that the FEV₁ is less likely to be influenced by upper airways mechanisms; (ii) experiments on animals have shown that, after methacholine challenge, firstly, effective lung compliance decreased,¹⁶ and secondly, lower respiratory reactance decreased but upper airways reactance remained unchanged.¹⁷ Thus, the upper airways response to methacholine might not contribute to the decrease in total reactance (conversely to respiratory resistance) and it is surmised that this feature could partly explain the significant correlation observed in our study between changes in FEV₁ and X5.

It has been established that changes in Zrs might be affected by an artifact due to the shunt of the extra-thoracic upper airways. Motion of the upper airway wall results in loss of flow leading to an underestimation of the impedance of the downstream respiratory system. This artifact could explain on the one hand, the relatively mild increase of R5 observed in responders during challenge in our study and on the other hand the low sensitivity values assessed for changes in R5 and X5. Our results are in accordance with those of Wilson et al.¹⁸ who reported, from a study that included 30 children aged 5 years, that in 12 subjects a fall in PtcO₂ of at least 15% occurred in the absence of a significant change in R6, concluding that FOT was unreliable in this age group. Most of the upper airway artifact may be eliminated if pressure is forced around the subject's head (head generator, HG) rather than directly at the mouth (standard generator, SG).¹⁹ It may be argued that the shunt impedance of the upper airway will remain constant throughout the bronchial challenge but Marchal et al.²⁰ observed that changes in resistance were generally larger with HG than SG while the changes in reactance were similar for both methods after challenge. They concluded that the HG method might improve the sensitivity of the FOT in evaluating bronchomotor response to methacholine in children. Desager et al.²¹ also found that HG impedance values

TABLE 4—Contingency Table Describing the Numbers of Subjects Correctly Classified as Positive or Negative for Bronchial Hyperresponsiveness by a 50% Increase in R5 and a 50% Decrease in X5 Versus the "Gold Standard" 20% Decrease in FEV₁ in the Overall Population

	Responders	Nonresponders
Increased R5	28	5
Non-increased R5	160	34
Decreased X5	68	6
Non-decreased X5	120	33

TABLE 5—Comparison Between Area Under the ROC Curves for Each IOS Parameter (Expressed as Percentage Change From Baseline Level)

	R5	R20	X5	f0	Z5
AUC	0.51	0.58	0.61	0.51	0.53
P*	0.65	0.18	0.01	0.48	0.37

AUC, area under curve.

*Degree of significance calculated by Wald's method.

were closer to the estimated lung impedance values than those of the SG technique. But they pointed out that because the head had to be enclosed in a box, the HG technique was nearly impossible to perform routinely in young children. As an alternative, Farre et al.²² proposed that assessing the change in oscillatory admittance (Ars), which is the reciprocal of Zrs, eliminated or markedly reduced the upper airway artifact when using the SG method.

In this retrospective study, the methodology was reproducible but possible methodological lack or bias should be considered: (i) because of time-constrained routine practice, we could not measure IOS parameters for each dose of methacholine and could not, therefore, analyze the dose-response relationship; (ii) the measurement of Zrs being performed when FEV₁ decreased by 20% or more, or after administration of the maximal dose, forced respiratory maneuvers could have induced changes in bronchial tone. Although different airway responses to a deep inhalation are described, bronchodilation usually occurs during methacholine challenge in healthy and mildly asthmatic subjects.²³ However, the strength of this bronchodilator effect should be put in perspective. Observations by Duiverman et al.⁴ in asthmatic children showed that the methacholine threshold and provocative doses were similar with maximal and partial flow-volume curves. Recently, it was demonstrated that deep inspiration-induced bronchoprotection was stronger

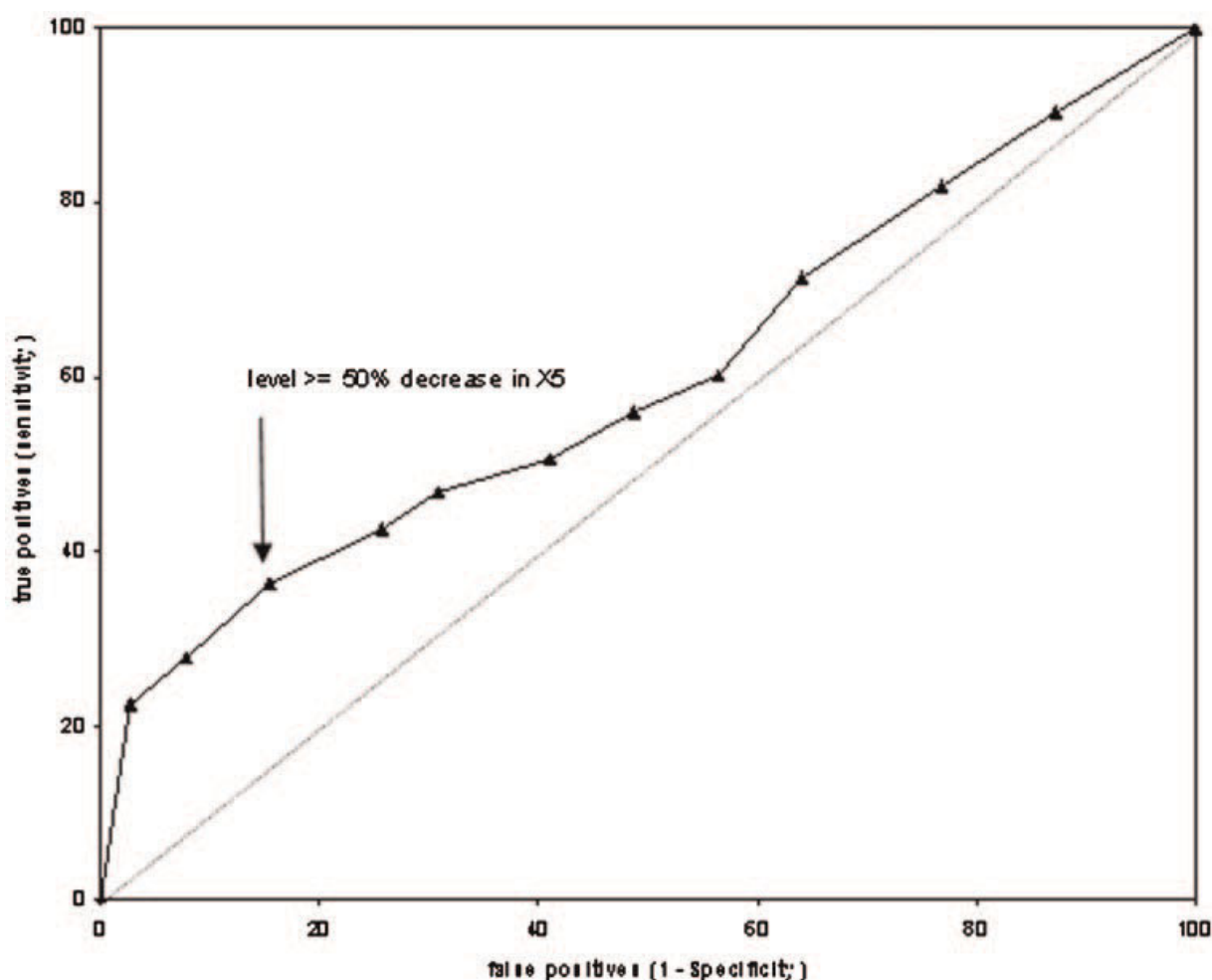


Fig 1. ROC curve describing relationship between sensitivity and specificity of changes in X5 to detect a 20% fall in FEV₁.

than bronchodilation in healthy subjects²⁴ and it also appeared that the protective effect of deep inspiration was more pronounced than the effect obtained if deep inspiration took place after the administration of methacholine.²⁵

CONCLUSION

In this study, the accuracy of measurements by means of IOS during methacholine bronchial challenge was not good when compared with FEV₁. A 50% decrease in X5 (especially if associated with an increase in Rrs) might be taken as an indicator of a bronchial response. It could be assumed that spirometry and IOS, while both providing indirect indices of airway patency, explore different mechanisms, each with its own methodological potentials and limitations.

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