Impulse oscillometry; a measure for airway obstruction
Abstract

The Impulse Oscillometry System (IOS) was introduced as a new technique to assess airflow obstruction in patients who are not able to perform forced breathing manoeuvres, like subjects with cerebral palsy, severe mental retardation and young children. This study evaluates the sensitivity and specificity of IOS parameters to quantify changes in airflow obstruction in comparison with FEV₁ and PEF measurements.

Measurements of FEV₁, PEF and Resistance (R) and Reactance (X) at frequencies of 5 to 35 Hz were performed in 19 children with asthma before, during and after methacholine challenge and subsequent bronchodilation. All parameters changed significantly during the tests. Values of R₅ and R₁₀ correlated with FEV₁ (r = -0.71, and -0.73, respectively, p<0.001), as did values of X₅ and X₁₀ (r = 0.52, and 0.57, respectively, p<0.01). Changes in R preceded changes in PEF and FEV₁ during methacholine challenge. The area under the Receiver Operating Characteristic curve to predict a 15% fall in FEV₁ showed better sensitivity and specificity for R₅ (area under the curve 0.85) compared to PEF (0.79) or R₁₀ (0.73).

We conclude that IOS parameters can be easily used as an indirect measure of airflow obstruction. This might be helpful in patients who are not able to perform forced breathing manoeuvres. In individual subjects, R values measured at 5 Hz showed to be superior to PEF measurements in the detection of a 15% fall in FEV₁.
Introduction

Lung function tests can often contribute to proper therapeutic strategies and follow-up of patients with lower respiratory illnesses. The forced expiratory volume in the first second (FEV₁) is regarded as the ‘gold standard’ for the assessment of airflow obstruction and general consensus exists about criteria for performance and standardization of this measurement¹. Unfortunately, some categories of patients, such as mentally retarded patients and young children, have a high risk for lower respiratory illnesses, but are not able to perform forced expiratory manoeuvres.

Respiratory disease is the major cause of death in children with cerebral palsy²-³, with a 140 fold increased mortality risk⁴. Because modern technologies for assessment of pulmonary function and treatment of pulmonary obstruction are not routinely applied in children with intellectual disability and young children, recognition and treatment of respiratory diseases might not be adequate in this group⁵. In young children the incidence of lower respiratory illnesses and wheezing is increasing⁶.

Children with severe neuromuscular disorders and children under the age of five rarely can generate forced expiratory manoeuvres that meet the above mentioned acceptability and reproducibility standards⁷. Also a relatively simple forced breathing test as peak expiratory flow (PEF) measurement is difficult to perform for these patients. During infancy several other lung function tests can be performed (e.g. partial flow volume curves, occlusion techniques), but most of these tests are limited to the first two years of life and can only be performed in research laboratories because of high technical requirements⁸. For large numbers of patients with lower respiratory illnesses lung function test facilities are very limited.

Recently, impulse oscillometry was introduced as a new technique for the assessment of airflow obstruction in children⁹. The Impulse Oscillometry System (IOS) does not require active co-operation of the patient and has become commercially available. The purpose of this study was to evaluate the sensitivity and specificity of IOS parameters to quantify changes in airflow obstruction. In order to compare the method with conventional forced breathing tests as the ‘gold standard’ for airflow obstruction, the study was performed in children who were able to perform FEV₁ and PEF measurements.
Subjects

We studied 19 children (7 boys) with asthma attending the outpatient paediatric pulmonology department of the Wilhelmina Children’s Hospital, Utrecht (age range 5 - 17 years). They all had moderate to severe asthma according to the International Consensus Report on Diagnosis and Treatment of Asthma10 and were treated with inhaled corticosteroids (beclomethasone dipropionate or budesonide 200-800 microgram daily) and rescue medication (salbutamol or terbutaline). All children were free of symptoms in the period of the study. All children had a baseline FEV1 of more than 70% of predicted. The children were not allowed to use bronchodilators during a period of at least 24 hours prior to the test. The study was approved by the Hospital Medical Ethics Committee, and informed consent from the parents was obtained prior to inclusion in the study.

Methods

Forced flow volume measurements

Maximal expiratory flow volume (MEFV) measurement was performed in all children, with use of a pneumotachometer system with Lilly head (MasterScreen Pneumo, Erich Jaeger, Germany). The best MEFV curve, according to the ATS criteria, from at least 3 trials was used1. Children who were not able to reach the ATS criteria of acceptability and reproducibility were not included into the study. All values were corrected to body temperature, ambient pressure saturated (BTPS) conditions. For reference values data of Zapletal were used11.

Peakflow measurements

Peak expiratory flow (PEF) was measured using a calibrated Wright spirometer (Clement Clarke International Ltd, London, UK). The children
were in a standing position and were instructed to exhale maximally after inhalation to total lung capacity. The best value of three repeated measurements was recorded.

**Impulse Oscillometry (IOS)**

The impedance of the total respiratory system was measured using a commercially available oscillometry system which has been described elsewhere\(^9\) (Masterlab-IOS, Erich Jaeger, Germany). During tidal breathing through a mouthpiece on a Y-piece an impulse generator produced brief pressure pulses at intervals of 0.2 sec. The power spectrum of the pulse was constant from 0 to 5 Hz and had a decrease of 20 dB in the range up to 40 Hz. These pressure fluctuations were superimposed on the spontaneous breathing pattern and were measured at the mouth by means of a differential pressure transducer with a total resistance below 50 Pa/l/sec and a pressure range of ± 1 kPa. The digitised pressure and flow signals were sampled at a rate of 200 Hz and were fed into a fast Fourier transformation, which transformed the complex pulse signals into their elementary sinusoidal components. The spectral ratio of the amplitude of the pressure wave signal to the resulting flow signal constituted the Impedance (Z) of the total respiratory system, from which the total resistance (R) and reactance (X) of the respiratory system were calculated\(^{12,13}\). In this study mean R and X values were calculated over a measurement period of 60 sec in the frequency range 5 - 35 Hz. During IOS measurement the children were sitting upright, their head resting against the back of the chair. They were instructed to breath quietly through a mouthpiece. To reduce loss of energy in the upper airways their cheeks and chin were supported by the hands of the investigator who was standing behind the patient.

**Study protocol**

After baseline IOS, FEV\(_1\) and PEF measurement methacholine challenge was performed according to a standardised protocol. Methacholine bromide aerosols were generated by calibrated DeVillbiss 646 nebulizers which were attached to a Rosenthal dosimeter. During quiet breathing from FRC to TLC the dosimeter was triggered. After performing baseline measurements normal saline was inhaled to rule out non-specific reactions and subse-
sequently methacholine was administered in doubling doses (3, 6, 12, 24, 50, 98, 196, 392 and 784 microgram methacholine). Three minutes after every dose of methacholine IOS, FEV<sub>1</sub> and PEF measurements were performed, each time in the same sequence. To prevent an unfavourable effect of deep inhalation on IOS parameters, IOS measurements were always performed immediately before FEV<sub>1</sub> and PEF measurements. Performance of all tests took 3 minutes. Provocation was continued until the dose at which FEV<sub>1</sub> had dropped 20% or more from baseline (PD<sub>20</sub>). After achieving PD<sub>20</sub> 400 microgram of salbutamol dose-aerosol was administered via a spacer device (Volumatic). Fifteen minutes after administration of salbutamol, all tests were performed in the same sequence as at baseline.

**Statistical analysis**

Distributions of parameters are summarised by mean (standard deviation), unless indicated otherwise. For comparison of paired data paired Student’s t-tests were used. To study the relationship between FEV<sub>1</sub>, PEF and IOS parameters Pearson’s correlation coefficients were calculated. Both for t-tests and correlation coefficients statistical significance was assumed if p-values were < 0.05. Changes in FEV<sub>1</sub>, PEF and R during methacholine challenge are expressed as percentage of baseline value. X values can not be expressed in this way, because these values range from negative to positive and cross the zero value in many children. In order to stratify the results of bronchial challenge for all children, the methacholine doses are expressed as the number of doubling doses prior to the maximal dose for each child. To describe the sensitivity and specificity of changes in PEF and IOS parameters in response to bronchial challenge in comparison to changes in FEV<sub>1</sub> receiver operating characteristic curves (ROC) were used. The area under the ROC curve is a measure for the overall discriminatory performance of a test.

**Results**

Mean age of the children was 10.5 (3.5) years, height 146.6 (19.8) cm and weight 42.5 (14.6) kg.
At baseline all children had normal lung function according to FEV$_1$ (mean 100.4 (17.1) % of predicted). After the maximal dose of methacholine FEV$_1$ fell significantly with simultaneously significant changes in PEF, R and X values at all frequencies (p < 0.001, Table 1). After inhalation of salbutamol all lung function parameters changed significantly compared to the post-challenge level (p < 0.001, Table 1). The largest changes in absolute values of R and X for both bronchoprovocation and bronchodilation were observed at the lower values of the frequency spectrum (especially at 5 and 10 Hz). No significant differences between baseline and post-bronchodilator values for any of the lung function parameters were observed (Table 1).

Results of Pearson correlation coefficients between the ‘gold standard’ FEV$_1$ and PEF and R and X values are shown in Table 2. PEF, R$_{5-35}$ and X$_{5-25}$ correlated significantly with FEV$_1$, but X$_{35}$ did not. The highest coefficients of correlation between FEV$_1$ and R and X values were seen at the lower frequencies (5, 10 and 15 Hz).

### Table 1. Values of FEV$_1$, PEF, R, and X at baseline after bronchial challenge and after subsequent bronchodilation in 19 children with mild to moderate asthma. All changes were significantly different from the prior level (all p values < 0.001).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>post-challenge</th>
<th>Post-bronchodilator</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$ (ml)</td>
<td>2251 (780)</td>
<td>1776 (639)</td>
<td>2351 (779)</td>
</tr>
<tr>
<td>PEF (ml)</td>
<td>2740 (873)</td>
<td>2310 (795)</td>
<td>2870 (869)</td>
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<td>R$_5$ (kPa/L/s)</td>
<td>.84 (.32)</td>
<td>1.27 (.36)</td>
<td>.70 (.29)</td>
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<td>R$_{10}$ (kPa/L/s)</td>
<td>.71 (.24)</td>
<td>.92 (.21)</td>
<td>.60 (.22)</td>
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<td>R$_{15}$ (kPa/L/s)</td>
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<td>.75 (.18)</td>
<td>.53 (.17)</td>
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<td>R$_{20}$ (kPa/L/s)</td>
<td>.57 (.19)</td>
<td>.67 (.17)</td>
<td>.50 (.15)</td>
</tr>
<tr>
<td>R$_{25}$ (kPa/L/s)</td>
<td>.54 (.17)</td>
<td>.63 (.16)</td>
<td>.50 (.13)</td>
</tr>
<tr>
<td>R$_{35}$ (kPa/L/s)</td>
<td>.54 (.16)</td>
<td>.63 (.15)</td>
<td>.51 (.13)</td>
</tr>
<tr>
<td>X$_5$ (kPa/L/s)</td>
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<td>-.35 (.25)</td>
<td>-.08 (.08)</td>
</tr>
<tr>
<td>X$_{10}$ (kPa/L/s)</td>
<td>-.13 (.12)</td>
<td>-.36 (.21)</td>
<td>-.08 (.10)</td>
</tr>
<tr>
<td>X$_{15}$ (kPa/L/s)</td>
<td>-.08 (.11)</td>
<td>-.26 (.14)</td>
<td>-.02 (.09)</td>
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<tr>
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<td>X$_{35}$ (kPa/L/s)</td>
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<td>.11 (.09)</td>
<td>.23 (.06)</td>
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</table>
Table 2. Pearson correlation coefficients between ‘gold standard’ measurements \( \text{FEV}_1 \) and \( \text{PEF} \), \( R \), and \( X \) values in 19 children with mild to moderate asthma.

|         | FEV\(_1\) | PEF  | R5  | R10 | R15 | R20 | R25  | R35  | X5  | X10 | X15 | X20 | X25 | X35 |
|---------|-----------|------|-----|-----|-----|-----|------|------|-----|-----|-----|-----|-----|-----|-----|
| PEF     |           |      |     |     |     |     |      |      |     |     |     |     |     |     |     |
| R5      |           | .83**|     |     |     |     |      |      |     |     |     |     |     |     |     |
| R10     |           |     | -.71**|     |     |     |      |      |     |     |     |     |     |     |     |
| R15     |           |     |     | -.73**|     |     |      |      |     |     |     |     |     |     |     |
| R20     |           |     |     |     | -.71**|     |      |      |     |     |     |     |     |     |     |
| R25     |           |     |     |     |     | -.70*|      |      |     |     |     |     |     |     |     |
| R35     |           |     |     |     |     |     | -.63*|      |     |     |     |     |     |     |     |
| X5      |           |     |     |     |     |     |      | -.65*|     |     |     |     |     |     |     |
| X10     |           |     |     |     |     |     |      |      | .52*|     |     |     |     |     |     |
| X15     |           |     |     |     |     |     |      |      |      | .57**|     |     |     |     |     |
| X20     |           |     |     |     |     |     |      |      |      |      | .58**|     |     |     |     |
| X25     |           |     |     |     |     |     |      |      |      |      |      | .58**|     |     |     |
| X35     |           |     |     |     |     |     |      |      |      |      |      |      | .51*|     |     |

** \( p < 0.001 \), * \( p < 0.01 \)

Figure 1. Relative changes in \( \text{FEV}_1 \), PEF, R5, and R10 (expressed as percentage change from baseline level) during methacholine challenge (expressed as number of doses prior to the maximal dose) and subsequent bronchodilation (after) in 14 children with a fall in \( \text{FEV}_1 \) of more than 20%. The open symbols represent changes statistically different from baseline value.
In 14 of all 19 children who completed the bronchial challenge test a more than 20% fall in FEV₁ was achieved (responders). The mean PD20 in these children was 98 microgram. In five children no threshold was achieved (non-responders). Figure 1 shows the relative changes during the challenge test of FEV₁, PEF and R₅ and R₁₀ (expressed as percentage of the absolute baseline value) of the responders. Figure 1 shows concomitant significant changes in FEV₁, PEF, and R₁₀ from methacholine dose max-2, while R₅ was already significantly increased from methacholine dose max-3. The rise in resistance (especially in R₅) values preceded the fall in FEV₁ and PEF. In the non-responders also concomitant changes in FEV₁, PEF, R₅ and R₁₀ were observed, but these changes were not statistically significant (except for R₅ at dose max-1).

Figure 2 shows the relationship between mean changes (expressed as relative changes compared to baseline values) in FEV₁ and in PEF, R₅ and R₁₀ during bronchoprovocation (negative changes) and bronchodilation (positive changes). This Figure shows a linear relationship between changes in FEV₁ and PEF, but a curvilinear relationship between changes in FEV₁ and R₅ and R₁₀.

*Figure 2. Relative changes in PEF, R₅, and R₁₀ (expressed as percentage change from baseline level) compared to the relative changes in FEV₁ during methacholine challenge and subsequent bronchodilation in 19 children with asthma.*
Figure 3. Receiver operating characteristic curve describing the relationship between sensitivity and specificity of changes in PEF, $R_5$, and $R_{10}$ to detect a 20% fall of $FEV_1$ during methacholine challenge.

Figure 4. Receiver operating characteristic curve describing the relationship between sensitivity and specificity of changes in PEF, $R_5$, and $R_{10}$ to detect a 15% fall of $FEV_1$ during methacholine challenge.
A ROC curve of the sensitivity and specificity of changes in PEF and R5 and R10 as a measure to detect a 20% fall in FEV₁ during bronchial challenge is shown in Figure 3. The area under the ROC curve for PEF > R5 > R10 (0.80, 0.75, and 0.68, respectively). Because this study showed that the rise in resistance values preceded the fall in FEV₁ and PEF (Figure 1) a second ROC curve was constructed, combining sensitivity and specificity of changes in PEF and R5 and R10 to predict a 15% fall in FEV₁ (Figure 4). The area under the ROC curve for R5 > PEF > R10 (0.85, 0.79, and 0.73, respectively). An increase in R5 of 50% to baseline showed an optimal combination of sensitivity and specificity to detect a 15% fall in FEV₁ (0.63 and 0.89, respectively).

Discussion

The present study showed significant changes in all lung function parameters after methacholine and salbutamol induced changes in airflow obstruction in children with asthma. Resistance (R) and reactance (X) values as measured with IOS were significantly correlated with the ‘gold standard’ FEV₁, R-values correlated better with FEV₁ than X-values. The sensitivity of R and X to experimentally induced changes in airway obstruction was best at the lowest frequencies, especially at 5 to 15 Hz. This study also showed that during bronchial challenge a rise in resistance values preceded the fall in FEV₁, which shows that both parameters are likely to reflect different pathophysiological aspects of airflow obstruction.

FEV₁ is a widely accepted and well standardised parameter of airflow obstruction⁴. In patients with neuromuscular diseases and in children under the age of five years, the parameter is often not useful, because FEV₁ measurement requires forced expiratory manoeuvres. These groups of patients lack co-ordination and co-operation. Kanengiser and Dozor showed that only 32% of children aged three to five years do meet the ATS criteria of reproducibility⁷. Therefore, in this study we studied children aged 5 to 17 years, to be sure of a reliable ‘gold standard’ for airflow obstruction. All children met the ATS criteria of acceptability and reproducibility⁴.
Home PEF meters are often recommended in monitoring airflow obstruction and bronchial hyperresponsiveness in patients with asthma\textsuperscript{15,16}. In this study PEF measurements were performed to compare the sensitivity and specificity of this well-known parameter with the values of the relatively new IOS parameters.

PEF values were strongly correlated with FEV\textsubscript{1} values (Table 2), and fell significantly after bronchial challenge and restored to baseline values after subsequent bronchodilation (Table 1). Changes in FEV\textsubscript{1} linearly correlated with somewhat smaller changes in PEF (Figure 2). These results show that PEF values can be easily used in population-based studies as a surrogate when FEV\textsubscript{1} is not available as a 'gold standard' for airway obstruction. However, in individual subjects the use of PEF values to detect a predefined level of airflow obstruction is hampered by suboptimal sensitivity and specificity of the parameter (Figures 3 and 4). The PEF results of the present study in children confirm the data from literature\textsuperscript{17} and are in line with findings in adults\textsuperscript{18}.

In this study results of a relatively recently described technique, the Impulse Oscillation System (IOS) were compared with results of forced breathing tests. The indices derived from IOS (R and X) are in principle comparable to those obtained by the pseudo random noise method of Landsèr and co-workers\textsuperscript{19}. This method has proved to be valuable for measuring lung function and bronchial hyperresponsiveness in young children\textsuperscript{20}. High technical requirements to the recording systems, energy loss in the upper airways and lack of sensitivity, especially at the higher frequencies impeded widespread use of oscillation techniques. Recently, the Impulse Oscillation System became commercially available and good sensitivity of R and X measured at 5Hz for methacholine induced lung function changes were described in 2-4 and 4-6-year-old children\textsuperscript{21,22}. The method is easy to perform and might be helpful as a routine diagnostic.

In this study significant changes in mean values of both R and X values at all frequencies were observed after bronchoprovocation and subsequent bronchodilation (Table 1). Significant correlation of R and X values with FEV\textsubscript{1} was observed, especially when measured at low frequencies (5 - 10 Hz) (Table 2). Other studies also showed that R and X values, especially R values at 5Hz were most sensitive to changes in airflow obstruction\textsuperscript{21-23}. In a recent study R\textsubscript{5} and X\textsubscript{5} values were used to study lung function in groups of young asthmatic children\textsuperscript{24}. These data show that IOS R and X values measured at 5 and 10 Hz can be useful in population-based studies, which can be attractive in patients who are not able to perform forced
breathing manoeuvres, like patients with neurological or muscular disorders and young children.

When lung function parameters are used to quantify changes in airflow obstruction, changes have to be expressed relative to baseline values. In children, lung function parameters are most time related to weight or height, and this also true for R5 and X5 values. Both deterioration (e.g. during bronchial challenge) and improvement (e.g. during reversibility testing) of lung function changes in children are to be expressed as a percentage of baseline values. In this study changes in R values but not in X values can be expressed in this way. X values range from negative to positive in many subjects (Table 1). Expression of changes in X-values as a percentage of baseline values would result in unrealistic or impossible numbers. For this reason only R values are helpful to quantify relative changes in individual subjects.

In this study a gradual increase in R values was observed during bronchial challenge both in children who reached a FEV1 related PD20 level (Figure 1) and those who did not. The increase in R values during the challenge in the non-responder group was not statistically significant (except for R5 at methacholine dose max -1). In the responder group, R values were already rising (R5 significantly at methacholine dose max -3) while FEV1 values were still unaffected (Figure 1). The relationship between changes in FEV1 and changes in R5 and R10 were further analysed in Figure 3. This Figure shows a curvilinear relationship between changes in FEV1 and R values, with large changes in R5 and R10 when FEV1 changes from 100 to 90% of baseline value and rather small changes of R5 and R10 when FEV1 further decreases from 90 to 80% of baseline value. The curvilinear relationship between changes in FEV1 and changes in R5 and R10, in contrast to a linear relationship between changes in FEV1 and PEF suggest that FEV1 and R values are likely to reflect different pathophysiological aspects of airflow obstruction. FEV1 is measured during maximal expiration from the maximal inspiratory lung volume, while R values are measured during tidal breathing. Airway resistance is known to be related to lung volume. Changes in FEV1 values are largely caused by changes in airflow limitation, while R values are more directly related to airway calibre.

The present study shows that the sensitivity and specificity of R5 and R10 to detect a 20% fall in ‘gold standard’ FEV1 do not exceed the performance of PEF values, resulting in a smaller area under the ROC curve (Figure 3). However our results showed that changes in R were more sensitive to detect smaller changes in FEV1 in subjects with normal baseline lung func-
The best combination of sensitivity and specificity to detect a 15% fall in FEV\(_1\) was observed when an increase of 50% compared to baseline R\(_5\) values was chosen as cut-off point. The area under the ROC curve for R\(_5\) (0.85) exceeded the area for PEF and R\(_{10}\) (0.79 and 0.73, respectively, Figure 4), but was also superior to the area under the curve for PEF in the detection of a 20% fall in FEV\(_1\) (0.80, Figure 3). These findings suggest that IOS R\(_5\) measurements can be used as a parameter in bronchial challenge testing in individual subjects with normal baseline lung function.

In conclusion, R and X values can easily be acquired using the IOS. They showed significant changes during changes in airflow obstruction and have significant correlation with FEV\(_1\). In groups of patients, R\(_5\) and X\(_5\) can be used as an indirect measure of airflow obstruction. In individual patients R\(_5\) showed to be superior to PEF measurements in the detection of a 15% fall in FEV\(_1\). Although the parameters do not exactly reflect the ‘gold standard’ FEV\(_1\), this technique might be helpful in patients who are not able to perform forced breathing manoeuvres.
References


