Comparison of changes in lung function measured by plethysmography and IOS after bronchoprovocation

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KEYWORDS
 Bronchoprovocation; Allergen challenge; Methacholine challenge; Spirometry; plethysmography; Impulse oscillation

Summary

Aim: Lung function tests are essential for the diagnosis and management of bronchial asthma. Impulse oscillation (IOS) system is an alternative way to measure lung mechanics for some patients. We investigated the relative sensitivities of IOS, body plethysmography and spirometry in detecting allergen- and methacholine-induced bronchoconstriction.

Method: Twenty-two subjects had single allergen inhalation and 8 subjects had 3 methacholine challenges. The tests were stopped when FEV₁ fell by 20%. Lung function was measured using IOS (R5, R20, R5-R20, X5, AX, fres), plethysmography (sRaw, sGaw, FRC, lung volumes) and spirometry (FEV₁, FVC, PEF, FEF₅₀%) during inhalation challenges, and expressed as percent change from pre-challenge baseline.

Results: All subjects were non-smoking adults with mild allergic asthma. Following allergen challenges, the most sensitive IOS index was R₅–R₂₀ and the most sensitive plethysmography and spirometry measurements were sRaw, sGaw and FEF₅₀%. Following methacholine challenge the most sensitive IOS index was AX, the most sensitive plethysmography measurement was sRaw. Overall, IOS (R₅–R₂₀, AX, X5 Hz) proved to be more sensitive than plethysmography and spirometry measurements following allergen-induced and methacholine-induced bronchoconstriction.

Conclusion: Our result shows that IOS is more sensitive than other lung function tests following allergen and methacholine challenge. In addition, IOS can act as an alternative measurement technique of airway resistance and obstruction in patients where manoeuvres involved in plethysmography and spirometry prove difficult to perform.

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Introduction

Bronchial asthma is most commonly evaluated using spirometric and plethysmographic measurements made at baseline, following bronchodilators or during bronchial provocation testing. For some patients such as children, institutionalized and frail elderly patients and those with difficulty performing forced respiratory manoeuvres, alternative tests have been suggested.1–3

There is a poor correlation between asthma, degree of airflow obstruction and FEV1,4,5 which is partly related to airway hyper-responsiveness (AHR), hyperinflation and fluctuation of FEV1. This suggests the need for a more sensitive test, such as impulse oscillometry, which may be used for better evaluation of lung mechanics particularly during methacholine-induced AHR.2,6–10

The forced oscillation technique (FOT) was introduced by Dubois and colleagues over 50 years ago as an alternative test to that of body plethysmography (sRaw, sGaw, FRC) and spirometry (FEV1, PEF, FEF50%) in detecting bronchoconstriction. We investigated the relative sensitivities of IOS, plethysmography and spirometry in adult asthmatic subjects following allergen-induced bronchoconstriction. We investigated the relative sensitivities of IOS (R5Hz, R20Hz, R5X5Hz, AX) to that of body plethysmography (sRaw, sGaw, FRC) and spirometry (FEV1, PEF, FEF50%) in detecting bronchoconstriction following allergen inhalation and methacholine challenge.

Methods

Subjects

Twenty-two subjects were recruited for single allergen inhalation challenges and 8 subjects were recruited for methacholine challenges. The study was approved by the institutional Research Ethics Board, and all subjects provided signed informed consent. Subjects were non-smoking adults with mild allergic asthma as defined by methacholine PC20≤16 mg/ml and FEV1 ≥70% predicted during a screening visit, and infrequent (< twice weekly) use of short-acting β2-agonists. Subjects were excluded if they had lower respiratory tract infection, asthma exacerbation within 4 weeks or used inhaled or oral steroids within 4 weeks. Short-acting β2-agonists were withheld 8 h before all visits and antihistamines were withheld 72 h before allergen challenges. Subject characteristics are shown in Tables 1 and 2.

Study design

This observational study was conducted to determine the relative sensitivity of IOS, plethysmography and spirometry in detecting allergen- and methacholine-induced bronchoconstriction. Following each inhalation period, measurements of IOS, plethysmography and spirometry were obtained, in this order, to avoid the effect of forced manoeuvres of plethysmography and spirometry on bronchial tone during IOS.

Impulse oscillometry

The impedance of the total respiratory system was measured using a MasterLab IOS system (Erich Jaeger Co, Wurtzburg, Germany). During tidal breathing for 30 s, an impulse generator produced brief pressure pulses (150 impulses) at intervals of 0.2 s and the pressure fluctuations were measured at the mouth. Subjects sat upright with, nose clip in place and hands supporting the cheeks. Mean resistance (R5, R20, R5–R20) Hz and reactance at 5 Hz (X5) reactance area (AX) and resonant frequency (fres) were calculated.
Body plethysmography

Measurements were made using a Vmax® SensorMedics® 6200 Autobox Dl. Total lung capacity (TLC), residual volume (RV), vital capacity (VC), inspiratory capacity (IC) and expiratory reserve volume (ERV) were measured by tidal breathing, and airway resistance (Raw), specific airway resistance (sRaw), conductance (Gaw), specific airway conductance (sGaw), functional residual capacity (FRC) and thoracic gas volume (Tgv) were measured while panting at 1 cycle per second with the airway occluded and unoccluded.

Spirometry

Spirometry was carried out using a Vmax® SensorMedics® 6200 Autobox Dl. The FEV₁, FVC, peak expiratory flow (PEF), forced expiratory flow (FEF₅₀%) and (FEF₇₅%) were measured and recorded. NHANES III predicted equations were utilized.

Part A — allergen challenge

Subjects recruited for the allergen challenges were skin prick tested to identify a suitable aeroallergen, and methacholine PC₂₀ was repeated at baseline on the day before allergen challenge in order to calculate the allergen dose for inhalation.²³ Allergen challenges were carried out by 2 min of tidal breathing doubling concentrations of allergen extract through a Hans Rudolph valve connected to a Wright nebulizer. Lung function was measured by IOS, plethysmography and spirometry, in this order, at baseline and 10 min after each dose of allergen. The challenge was stopped when the FEV₁ fell by 20% from the pre-allergen baseline.²⁴ Lung function was then measured by IOS, plethysmography and spirometry at 20, 30, 45, 60 and 90 min, then hourly up to 7 h post-allergen challenge. The early asthmatic response (EAR) was measured for up to 3 h post-allergen and the late phase response (LAR) was measured between 3 and 7 h post-allergen challenge.

Table 1: Demographic details of the subjects undergoing methacholine challenges.

<table>
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<tr>
<th>Subject</th>
<th>Sex (M/F)</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>FEV₁ (%pred)</th>
<th>Methacholine PC₂₀ (mg/ml)</th>
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Mean ± SD 13 F, 9 M 25 ± 10 171 ± 8 68 ± 12 90 ± 14 2.69 (0.29–19.35) 29 ± 10 12 ± 13

Table 2: Demographic details of the subjects undergoing allergen challenges.

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<th>Age (years)</th>
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Comparison of changes in lung function 505
allergen. The maximum percent fall in FEV\(_1\) was calculated for the EAR and LAR (Table 1).

**Part B – methacholine challenge**

Subjects attended a screening visit for a medical assessment and screening methacholine challenge to determine the presence and severity of airway hyperresponsiveness (PC\(_{20}\)). At the next visit subjects had pulmonary function measured by IOS, plethysmography and spirometry (in this order), at baseline and again after each concentration of provocholine. Methacholine challenges were carried out by 2 min tidal breathing of doubling concentrations of provocholine through a Hans Rudolph valve connected to a Wright nebulizer. IOS was performed 30–60 s post-inhalation, plethysmography was performed 1.5–2 min post-inhalation, and spirometry was performed approximately 2 min post-inhalation. Each inhalation of methacholine was separated by 5 min. The test was terminated when the FEV\(_1\) fell by 20%.

**Analysis of results**

Following increasing doses of methacholine or allergen, resistance progressively increased and flow rate progressively decreased. Summary statistics are presented as mean ± standard deviation, unless otherwise noted. The relative sensitivity of the change in lung function post-challenge was measured in an ordinal fashion. All values were transformed and expressed as a fraction of the value at baseline to allow comparison, the ordinate then was expressed on a log scale such that a 50% reduction in flow rate from control (0.5) is equivalent to a doubling of resistance from control (2.0). The ordinates were then plotted against time (for allergen challenges) or % change in FEV\(_1\) (for methacholine challenges). Sensitivity was defined by the number of units above or below baseline and sensitivities were rank ordered.

**Results**

**Part A: allergen challenge**

Twenty-two subjects inhaled an allergen to which they were sensitized and the mean maximum % fall in FEV\(_1\) during the early response was 29 ± 10%; 20 subjects had a maximum % fall in FEV\(_1\) during the early response of ≥20% from baseline and in two subjects the maximum % fall in FEV\(_1\) during the early response was between 15% and 20%. Six subjects developed a late asthmatic response, as defined by a maximum % fall in FEV\(_1\) of ≥15% between 3 and 7 h post-challenge. The mean maximum % fall in FEV\(_1\) between 3 and 7 h post-allergen was 12 ± 13% (Table 1).

The relative sensitivity of spirometry measurements is shown in Fig. 1. The FEF\(_{25-75}\) was the most sensitive spirometric measurement recorded during both the early and late asthmatic responses, with relative sensitivity reaching 0.57 ± 0.14 and 0.81 ± 0.13, respectively, which was similar to the FEF\(_{25-75}\) (Fig. 1) and FEF\(_{75}\) (data not shown). Forced expiratory mid-flow rates were more sensitive than the FEV\(_1\), which had a relative sensitivity reaching only

**Figure 1** Mean (±95% confidence intervals) relative sensitivities of spirometry measurements until 7 h following allergen challenge expressed as a fold change from baseline.

0.74 ± 0.11 and 0.87 ± 0.16 during the early and late responses, respectively. The PEF had a similar sensitivity to the FEV\(_1\), and the FVC was considerably less sensitive with sensitivity values close to 1 (Fig. 1).

Measurements of plethysmography demonstrate that sRaw and sGaw are more sensitive than RV, FRC and TLC (Fig. 2), VC, IC, Raw, Gaw and Vtg (data not shown) to detect allergen-induced changes in lung function during the early and late asthmatic responses. Furthermore, sRaw and sGaw have higher sensitivity values (farther from a value of 1) than the mid-flow rates measured by spirometry.

The relative sensitivities of IOS measurements following allergen challenge are shown in Fig. 3. Measurements of R\(_{5Hz}\), R\(_{20Hz}\), AX and sGaw have higher sensitivity values (farther from a value of 1) than the mid-flow rates measured by spirometry.

The relative sensitivities of IOS measurements following allergen challenge are shown in Fig. 3. Measurements of R\(_{5Hz}\), R\(_{20Hz}\), AX and sGaw have higher sensitivity values (farther from a value of 1) than the mid-flow rates measured by spirometry.

**Part B: methacholine challenge**

Eight subjects had methacholine challenges. The mean FEV\(_1\)% at baseline was 88 ± 11.3%, and the mean provocative concentration of methacholine causing 20% fall in FEV\(_1\) (PC\(_{20}\)) was 4.62 mg/ml. 3 subjects had PC\(_{20}\) < 4 mg/ml, 2 subjects had PC\(_{20}\) between 4 and 8 mg/ml and 3 subjects had PC\(_{20}\) between 8 and 16 mg/ml (Table 2). The relative

**Figure 2** Mean (±95% confidence intervals) relative sensitivities of plethysmography measurements until 7 h following allergen challenge expressed as a fold change from baseline.
sensitivities of spirometry measurements during methacholine challenge are shown in Fig. 4. FEF_{50\%} and FEF_{25–75\%} were the most sensitive spirometry measurements compared to % fall in FEV_{1}, with relative sensitivity reaching 0.56 ± 0.09 and 0.57 ± 0.04, respectively, the sensitivity of PEF was similar to FEV_{1}. The least sensitive measurement was FVC which was close to 1 (0.87 ± 0.04). Measurements of plethysmography also demonstrate that sRaw and sGaw are more sensitive than RV, FRC and TLC (Fig. 5), VC, IC, Raw, Gaw and Vtg (data not shown) to detect methacholine-induced bronchoconstriction and that sRaw and sGaw have higher sensitivity values (farther from a value of 1) than the mid-flow rates measured by spirometry.

The relative sensitivities of IOS measurements following methacholine challenge are shown in Fig. 6. Measurements of AX and R5-R20 Hz have the highest sensitivity of all other measurements, being 3–4 times higher than sRaw and sGaw. The least sensitive IOS measurements were R5 Hz, R20 Hz, fres and X5Hz (data not shown). Baseline values for spirometry, plethysmography and IOS for subjects undergoing allergen and methacholine challenges are shown in Table 3.

Discussion

The purpose of this study was to investigate the relative sensitivities of IOS, body plethysmography and spirometry in detecting bronchoconstriction following allergen and methacholine challenges. Twenty-two atopic asthmatics underwent allergen challenge and were then assessed with pulmonary function testing (IOS, body plethysmography and spirometry); measurements were then compared during EAR and LAR. Eight asthmatics underwent 3 methacholine challenges with similar lung function tests measured after each dose. R5-R20 and AX were the most sensitive indices of bronchoconstriction and R20Hz was the least sensitive index. For plethysmography and spirometry; sRaw followed by sGaw and then FEF_{50\%} were the most sensitive measurements compared to FEV_{1}. Overall, IOS measurements proved to be more sensitive measures of bronchoconstriction than those of both plethysmography and spirometry.

Current ATS criteria rely on measuring FEV_{1} to diagnose asthma. However, there are many drawbacks to this. Many patients have normal spirometry at the time of assessment require methacholine challenge to make the diagnosis. Therefore, ATS criteria are not suitable for many asthma patients whose FEV_{1} values are close to normal.^{25–27} Also, spirometry and body plethysmography require active patient cooperation and may, therefore be difficult for some patients to perform.^{1–3} In addition, performing forced manoeuvres to measure the FEV_{1} influences bronchial tone. IOS was introduced as an alternative way to measure the mechanics of the respiratory system. Previous studies have demonstrated an increased sensitivity of IOS compared to
spirometry, and compared to spirometry and plethysmography following bronchodilator administration in stable asthmatics. Our results are consistent with these studies: we found IOS measurements to be more sensitive than spirometry and body plethysmography measurements in detecting both allergen- and methacholine-induced bronchoconstriction. The increased sensitivity of IOS holds promise for its use in bronchoprovocation tests, where it can decrease the duration of test times and doses required to induce bronchoconstriction, thereby making the tests faster and “safer” for patients. Until the reliability of IOS as well as standardized guidelines of its usage can be better established, IOS should not be interchangeable with that of plethysmography or spirometry. However, IOS can act as an alternative measurement technique of airway resistance and obstruction for certain categories of patients, where manoeuvres involved in plethysmography and spirometry prove difficult to perform.

Investigation of the role of small airways in asthma has previously lagged because of the difficulty in assessing this area. We have since come a long way, as with the help of newer techniques, airway inflammation, remodelling and functional changes have all been well documented in the small airways.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Mean (SD) baseline spirometry, plethysmography and IOS values for subjects undergoing methacholine and allergen challenges.</th>
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<td>FVC</td>
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<td>PEF</td>
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<td>FEF25%75%</td>
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<td>FEF50%</td>
<td>4.44(0.93)</td>
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During airflow obstruction, the pulmonary resistance at the low frequency of 5 Hz is much higher than that of the higher frequency at 20 Hz, and this reflected by an increased resistance at R5—20 Hz. Our results are consistent with other studies suggesting that R5—20 Hz and AX reflect small airway resistance and are closely related to methacholine-induced bronchoconstriction. R5—20 Hz and AX were more sensitive than R5 Hz, which correlated poorly with changes in FEV1, and there was no change in R20 Hz reflecting no change in proximal airway obstruction. These observations suggest that methacholine-induced symptoms are associated with distal airway heterogeneity, and are supported by other studies showing a higher sensitivity of R5-R20 and AX in monitoring bronchoconstriction and responses to therapy. We demonstrated that R5 Hz was the least sensitive index compared to FEV1. In contrast, the PC40-Rrs 6 Hz measured by forced oscillation in an earlier report was found to shorten the duration of methacholine challenge and allow lower doses of methacholine to be delivered compared to
PC20 FEVs1.14 Methodological differences could contribute to this apparent difference, including generation of larger particles by the DeVilbiss nebulizer with preferential deposition in the larger or medium-sized airway, thus increasing resistance at Rs 6 Hz.

In addition, R20Hz, a proposed measure of large airway obstruction,42 was the least sensitive index in the current study. This was not surprising, as previous studies showed that patients with airflow obstruction could be identified by most IOS parameters except for R20 Hz.43 These findings collectively suggest that peripheral airways may play a significant role in methacholine-induced bronchoconstriction, and during EAR and LAR in allergen-induced asthma. The LAR, thought to result from the infiltration of inflammatory cells and its consequences (e.g., mucus secretion and oedema) into the airways, has been suggested to preferentially occur in the small airways.44 Also, Zeidler et al. demonstrated worsening small airway obstruction (as indicated by lower lung attenuation measured by high resolution CT and an increased closing volume) in atopic asthmatics at 6 and 23 h after exposure to natural cat allergen, corresponding to the LAR and possibly resulting from small airway inflammation.45 Our results are consistent with these studies. The EAR, however, results primarily from the cellular release of histamine and lipid mediators and their subsequent binding receptors on airway smooth muscle. Histamine-responsive receptors mainly reside in the large airways46 however, we observed no changes in R5 Hz or R20 Hz. In contrast, we observed an increase in resistance at R5–R20 Hz during EAR, which may reflect the effects of cysteinyl leukotrienes binding to receptors in the small airways.47 More investigation into the roles of large versus small airways in allergen-induced asthma is required.

Our findings of increasing resistance in the smaller airways during bronchoprovocation with methacholine and allergen is consistent with previous work, and IOS measurements have shown to be consistently more sensitive than those of plethysmography and spirometry. Clinically, IOS could be implemented in patients unable to perform spirometry, and may reduce the time and dose of challenge agent, thereby making the procedure safer. However, IOS should not be interchangeable with that of plethysmography or spirometry until the reliability, correlation to clinical disease and disease severity, and standardized guidelines for IOS are established.

Conflict of interest

The authors declare that there are no conflicts of interest.

References