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Methacholine-induced asthma symptoms correlate with impulse oscillometry but not spirometry ☆

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Summary
Previous studies showed poor correlation between asthma symptoms and spirometric-based bronchial provocation tests. Use of impulse oscillometry (IOS) in airways resistance measurement may be more sensitive. In 20 individuals with stable asthma, we analysed the relationship between methacholine-induced asthma symptoms scores, IOS and spirometry. Following a screening visit, methacholine challenge testing was performed twice (visits 1 and 2). Dyspnoea, tightness and wheeze were quantified using visual analogue scores. IOS and spirometry were conducted at each incremental dose of methacholine. The Pearson correlation coefficient and linear regression analyses were conducted to explore the relations. A significant correlation was observed between methacholine-induced dyspnoea scores and the change in IOS measures of R_5 ($r = 0.62$, $p = 0.004$) and X_5 ($r = 0.51$, $p = 0.022$), but not with the spirometric changes in FEV_1 ($r = 0.37$, $p = 0.11$) or MEF_{50} ($r = 0.32$, $p = 0.17$). In a multiple linear regression model, R_5 was the only significant variable to explain dyspnoea variability ($p = 0.003$). Results of correlation analyses for chest tightness were similar to those obtained with dyspnoea. However, the symptom of wheeze showed correlation with IOS and spirometry. We conclude that airway resistance measured by IOS during methacholine challenge correlates better with asthma symptoms than traditional spirometric measures implying a higher sensitivity index.

Introduction

Spirometry-based non-specific provocation tests are widely used in measurement of airway hyper-responsiveness, asthma diagnosis, and in some instances to guide treatment. However, studies have shown poor correlation between histamine or methacholine-induced asthma symptoms (e.g.

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dyspnoea) and degree of airway obstruction as measured by the fall in forced expiratory volume in 1 s (FEV_1).[1,2] This is contributed to by the considerable variation in perception of symptoms such as dyspnoea between individuals with asthma. The expression of dyspnoea in asthma is related to an interplay of complex mechanisms, including change in lung volume, speed of bronchoconstriction, anxiety level, duration of asthma and age, attitudes, expectation and personality traits.[3,4] In some situations, the importance of these factors varies according to the method used to induce bronchoconstriction. For instance, in histamine and methacholine-induced asthma symptoms, the speed of bronchoconstriction and associated lung hyperinflation seem to play an important part.[4,5] Consequently, the lack of good correlation between methacholine-induced asthma symptoms and traditional measurement of bronchoconstriction (e.g. FEV_1) is not surprising.

The forced oscillation technique (FOT) was introduced as a technique for the assessment of respiratory mechanics by Dubois et al.[6] It employs small-amplitude pressure oscillations over a wide range of frequencies superimposed on normal breathing and has the advantage over conventional lung function techniques that it does not require the performance of active respiratory manoeuvres. It measures pulmonary impedance by sending a sound wave produced by an impulse generator through a mouthpiece during tidal breathing. The spectral ratio of the amplitude of the pressure wave signal to the resulting flow signal constitutes the impedance (Z) of the total respiratory system, through which the total resistance (R_{rs}) and reactance (X_{rs}) of the total respiratory system is also calculated.[7,8] The clinical potential of the method became apparent because it is rapid, demands only passive cooperation (no active breathing manoeuvres), is non-invasive, and is particularly suitable for use in children and in patients with poor coordination.[9]

The FOT has proved its usefulness in clinical practice and in instances its superiority to spirometry.[10] The sensitivity of R_{rs} and X_{rs} values to experimentally induced changes in airway obstruction appear to be better at lower frequencies, especially at 5–15 Hz, where an earlier rise in resistance values has been observed to precede the fall in FEV_1.[9,11] Several mechanisms may account for these differences, including the need for deep inspiration prior to spirometry which may alter bronchial tone in asthma.[12] The influence of the lung volume at which R_{rs} and X_{rs} are measured may also play a role, particularly in the bronchial challenge setting where a resulting increase in lung volume due to bronchoconstriction contributes to R_{rs} and X_{rs} values.[13]

The Jaeger impulse oscillation system (impulse oscillometry (IOS), Erich Jaeger, Hoechberg, Germnay) has been introduced as user-friendly commercial version of the FOT. IOS is however, different from the classical FOT because an impulse (a rectangular wave form) rather than a pseudorandom noise signal (a mixture of several sinusoidal wave forms) is applied by a loud speaker, and because of differences in data processing (e.g. use of coherence function in data acceptance and implementation of simple models simulating mechanics of the central and peripheral parts of respiratory system). A limited number of studies have been published on IOS accuracy compared to FOT, which generally suggest that the two methods yield similar but not identical measures of R_{rs} and X_{rs}.[22] However, in the context of methacholine challenge, there is no available published comparison between IOS and the gold standard spirometry-based FEV_1.

This study examines the hypothesis that symptom scores in patients with asthma following methacholine challenge show a different relationship with IOS indices than with spirometric-based measurements.

Methods

Subjects

Twenty participants with established doctor-diagnosed asthma of at least 2 years who had demonstrated either reversible airway disease or bronchial hyper responsiveness with a $PC_{20} \leqslant 16$ mg/ml to methacholine, were invited to participate. Airway reversibility was defined by either an increase in $FEV_1 \geqslant 12\%$ after inhaled short-acting β agonist, salbutamol (400 μg), or a variation of peak flow of $\geqslant 20\%$ over 50% of time in 2-week period within the previous 12 months. Subjects were aged between 18 and 65 years, had stable mild to moderate asthma (daily inhaled corticosteroid dose of $\leqslant 1000$ μg beclomethasone dipropionate or equivalent), and had an $FEV_1 \geqslant 75\%$ predicted. Participants who had experienced an exacerbation needing oral corticosteroid treatment within 4 weeks of the screening visit were excluded. The East Birmingham Local Ethics Committee, UK, approved the study. All patients gave informed written consent.

Study design

Participants attended an initial screening review in which their asthma diagnosis, severity, medication level and symptoms stability were assessed. Visit 1 was conducted a week afterwards in which participants undertook baseline visual analogue score (VAS), IOS measures and flow-volume loops in that order. Methacholine challenge was then conducted with measurement of IOS and flow-volume loops at each doubling dose of methacholine. VAS, IOS and flow-volume loops were measured immediately after challenge. To assess reproducibility, the same protocol was repeated 2–3 weeks afterwards at visit 2 having had no respiratory tract infections, or changed asthma status in the intervening period, to augment test repeatability.

Impulse oscillometry (IOS)

The IOS MasterScreen device (E. Jaeger GmbH, Wurzburg, Germany) consists of a loudspeaker as a pulse generator to send the pressure impulses to the respiratory system.[14] During tidal breathing, through a plastic mouthpiece, the impulse generator produces brief pressure pulses at intervals of 0.2 s. The superimposed pressure oscillations during normal spontaneous breathing are composed of several frequencies allowing assessment of R and X at several frequencies simultaneously. A fast Fourier analyser is employed within the system to determine R_{rs} and X_{rs} at these frequencies. The impedance (Z_{rs}) representing a

complex airway resistance, which includes two components, the real resistance (R_{rs}) and the imaginary reactance (X_{rs}), has also been determined. The frequency range of the signal was from 0 to 100 Hz, and we recorded R_{5-20} and X_5. R_{rs} at 5 and 20 Hz represent the low (total resistance) and high (central resistance) frequency range, respectively. In this asthmatic group, the low frequency R_5 was used as primary parameter on the basis of previous studies reporting its reliability in assessing bronchial responsiveness.[15]

During IOS measurements subjects sat upright with the head in neutral position, and a nose clip in place, while supporting their cheeks with their hands.[15] Monitoring took place for 30 s over a few respiratory cycles of quiet breathing and when the subjects got used to the forcing signal, baseline impedance measurements were recorded over 30 s before challenge testing. The results were averaged over the entire 30 s during which 150 impulses were applied. IOS measurements were systematically applied prior to any forced respiratory manoeuvre and repeated in the same order after each methacholine challenge step.

Forced flow volume measurements

Before bronchial challenge testing maximal flow volume measurements were performed using a Jaeger-Masterlab (E. Jaeger GmbH, Wurzburg, Germany). The following parameters were measured: FEV_1, and the maximal expiratory flows at 25%, 50% and 75% of vital capacity (MEF_{25}, MEF_{50}, and MEF_{75}), using the European Community for Coal and Steel normal values.[16] The largest FEV_1 value from three acceptable manoeuvres was used as the baseline FEV_1.[17]

Visual analogue score (VAS)

A VAS was used to assess dyspnoea, tightness and wheeze at the start and end of the methacholine challenge.[18] Subjects were instructed to score for each symptom without being able to see the score they had recorded at any previous time point.

Methacholine challenge

Subjects abstained from using β_2-agonist inhalers (6–12 h), oral β_2-agonist (24 h), cromolyns (24 h), xanthines (24 h), and anti-cholinergics (8–24 h) prior to challenge. Subjects were administered a methacholine aerosol inhalation test according to a 5 breath dosimeter protocol.[19] After baseline measurements of IOS and spirometry in that order, subjects inhaled one bolus of 0.9% saline followed by increasing doses of methacholine (saline, 0.0625, 0.25, 1, 4, 16, and 32 mg/ml) at no greater than 3 min intervals. IOS measurements were repeated at 60 s and spirometry at 90 s after each inhalation dose. The test was stopped: (a) following a decrease of $>20\%$ in the FEV_1; (b) when the maximal provocation concentration of 32 mg/ml was reached; and (c) if the subject felt symptomatically unwell.

Statistical analysis

Statistical analysis used SPSS version 10.0 (Chicago, USA). Distribution parameters were summarised by minimum and maximum values range, mean and standard deviation (SD) unless indicated otherwise. To confirm a significant effect of provocation testing on VAS, IOS, and spirometry parameters, differences between post- and pre-challenge values were calculated for visits 1 and 2. The mean of differences (Δdyspnoea, Δtightness, Δwheeze, ΔR_5, ΔX_5, ΔFEV_1, and ΔMEF_{50}), were tested by being different from zero by the paired t-test and the Wilcoxon matched-pairs test. Repeatability of the values of Δdyspnoea, Δtightness, Δwheeze, ΔR_5, ΔX_5, ΔFEV_1, and ΔMEF_{50} between visits 1 and 2, was analysed by Bland and Altman plots using MedCalc® version 9.0.1.0 (www.medcalc.be).[35]

To study the relationships between VAS, IOS and spirometry parameters, Pearson's correlation coefficients were calculated. In this analysis, the change in FEV_1 and MEF_{50} values from baseline to end of methacholine challenge were expressed as a percentage "$\%\Delta$ = baseline—post-challenge/baseline $\times$ 100", while for R_5 and X_5 values the $\%\Delta$ is calculated as "post-challenge—baseline/baseline $\times$ 100". For dyspnoea, tightness and wheeze the Δ value was used as it represents a pre- and post-challenge change across a 100 mm visual scale.

Stepwise forward linear regression analysis between the dependent variable "Δdyspnoea" and co-variables ΔR_5, ΔX_5, ΔFEV_1, and ΔMEF_{50} was also conducted to explore the co-variables that fit the model best. Statistical significance was assumed if p-values were <0.05.

Results

Subjects characteristics

Twenty participants met the inclusion criteria and underwent methacholine challenges on two occasions. Their clinical details are summarised in Table 1. The mean results of visits 1 and 2 bronchial challenges are shown in Table 2. Bland Altman plots display the repeatability of these results (Figure 1). Allowing for outliers the results of VAS, IOS, and spirometry revealed repeatable results to within 2 SDs on both sides of the arithmetic mean (Figure 2).

Overall there were statistically significant increases in values of dyspnoea, tightness, wheeze, R_5, X_5, and decreases in FEV_1 and MEF_{50} ($p<0.001$) following challenge. In visit 1, all but five individuals achieved FEV_1 PC_{20} of <32 mg/ml. In four subjects, the challenge was discontinued prematurely due to development of significant asthma symptoms. Their provocation results were $PC_{18.7}$ at 4 mg/ml, $PC_{16.4}$ at 0.25 mg/ml, $PC_{18.7}$ at 4 mg/ml and $PC_{17.5}$ at 4 mg/ml. However, three of them achieved PC_{20} <16 mg/ml in visit 2, but the fourth subject's challenge was discontinued prematurely again at $PC_{13.1}$ (16 mg/ml) due to worsening symptoms. The fifth individual's PC_{20} was >32 mg/ml with FEV_1 drop of 14.1% and 18.6% in visits 1 and 2, respectively. She has an established diagnosis of asthma since childhood, which is treated with seretide (fluticasone 100 mcg/salmeterol 50 mcg) 2 doses twice a day and salbutamol as required.

Twelve subjects were receiving inhaled corticosteroids, ICS (mean dose = 809 μg beclomethasone equivalent), while the remaining 8 were not receiving ICS. We observed no difference in symptom scores, spirometry or IOS measurement between steroid naïve and steroid treated groups (data not shown).

Correlation between symptoms and lung function indices

Results are shown in Table 3. Dyspnoea scores correlated closely with symptoms of chest tightness ($r = 0.94$) and wheeze ($r = 0.80$), and with IOS measurements (for R_5, $r = 0.63$, X_5, $r = 0.60$ and Z_5 $r = 0.68$; p values for all <0.01), but not with FEV_1 ($r = 0.37$, $p > 0.05$) or MEF_{50} ($r = 0.35$, $p > 0.05$). However, FEV_1 and MEF_{50} showed weak but significant correlations with wheeze. Changes in the IOS measurement R_5 preceded change in spirometry (FEV_1) during the methacholine challenge (data not shown).

We observed no significant correlation between R_5 and spirometry measurements, however, X_5 showed a weak but statistically significant correlation with FEV_1 ($r = 0.45$, $p < 0.05$) and MEF_{50} ($r = 0.47$, $p < 0.05$).

Table 1 Demographic details of the subjects.

Patient characteristics	Range (mean–SD)
Age in years	18–62 (34.5 ± 11.2)
Height (cm)	147–183 (162 ± 8)
Weight (kg)	51–98.4 (66.76 ± 12.7)
Sex (m/f)	3/17
Tobacco pack years	0.0–1.0 (0.11)
FEV_1 (% pred)	78.5–135.7 (99.7 ± 17.2)
MEF50 (% pred)	39.7–131.7 (70.6 ± 23.3)
FEV_1/FVC	60.8–93.4 (80.4 ± 9.4)
ICS (μg)*	0–1000 (485 ± 412)

Values are presented as minimum–maximum range (mean ± SD). Relative values of spirometry parameters are given as percentage of the predicted value (% pred).
Abbreviations: FEV_1: forced expiratory volume in 1 s; MEF_{50}: maximal expiratory flow at 50% of vital capacity; ICS: inhaled corticosteroids.
*Concurrent treatment dose of beclomethasone dipropionate or equivalent.

Linear regression analysis

Linear regression of post-challenge change in dyspnoea scores (Δ dyspnoea) on % post-challenge increase in R_5 ($\%\Delta R_5$) showed a significantly positive relationship ($p = 0.004$, $R^2 = 0.38$). Conversely, the relationship between Δ dyspnoea and % post-challenge decrease in FEV_1 ($\%\Delta FEV_1$) using linear regression was not significant ($R^2 = 0.14$, $p = 0.11$) (Figure 1).

In a forward stepwise multiple linear regression model, co-variables, which would explain the dependent variable "dyspnoea" were explored. R_5 showed the most significant slope ($p = 0.003$), while the addition of the other co-variables was not statistically significant (Table 4).

Discussion

In patients with well-established and stable asthma, we investigated the relationship between methacholine-induced asthma symptoms scores, IOS measured resistance (R_{rs}) and reactance (X_{rs}), and the spirometry derived "gold standard" FEV_1 and MEF_{50}. We demonstrated a significant correlation between dyspnoea scores and IOS but not with spirometry. To our knowledge, this is the first study that has examined the correlation between IOS indices and asthma symptoms as a primary outcome following methacholine challenge.

Both R_5 and X_5 correlated significantly with methacholine-induced dyspnoea, tightness and wheeze, while FEV_1 and MEF_{50} showed no significant correlation except for a borderline correlation with wheeze. Post-methacholine-induced dyspnoea showed a closer relationship with tightness than wheeze. Indeed, the correlation pattern of

Table 2 Methacholine challenge results for visits 1 and 2.

	Visit 1				Visit 2				Repeatability
	Pre	Post	Δ	% Δ	Pre	Post	Δ	%Δ	
Dyspnoea	3.2 ± 5.6	35.5 ± 26.3	32.5 ± 26.7		7.5 ± 18	36.4 ± 28.5	35.2 ± 28.5		27.8
Tightness	6.7 ± 8.4	41.0 ± 24.8	34.4 ± 25.5		5.4 ± 7.3	44.7 ± 25.8	39.3 ± 25.5		31.7
Wheeze	4.4 ± 8.8	31.4 ± 22.8	27.0 ± 25.4		3.6 ± 7.6	30.1 ± 25.1	30.5 ± 26.7		26.1
R_5 (kPa/l/s)	0.48 ± 0.17	0.75 ± 0.2	0.27 ± 0.17	61.7 ± 37.4	0.48 ± 0.16	0.77 ± 0.2	0.29 ± 0.17	64.5 ± 38.4	54.5%
X_5 (kPa/l/s)	−0.18 ± 0.1	−0.34 ± 0.3	0.16 ± 0.24	84.8 ± 65.6	−0.15 ± 0.1	−0.36 ± 0.23	0.21 ± 0.15	150 ± 112	182.3%
FEV_1 (l)	2.9 ± 0.5	2.2 ± 0.4	0.68 ± 0.27	23.7 ± 8.0	2.9 ± 0.6	2.1 ± 0.5	0.76 ± 0.4	22.7 ± 9.8	16.9%
MEF_{50} (l/s)	3.0 ± 1.0	2.0 ± 0.7	1.1 ± 0.57	38.8 ± 22.7	3.0 ± 1.1	1.9 ± 0.8	1.14 ± 0.86	37.3 ± 17.9	33.0%

Results are shown as means ± standard deviation for pre- and post-methacholine challenge values and the difference between the two (Δ) and its percentage (%Δ). The dyspnoea, tightness and wheeze values represent actual change on a 100 mm scale between "pre"- and "post"-methacholine challenge measurements, therefore no percentage was calculated. Measurement of error "repeatability" of visits 1 and 2 for measured parameters is also given.[36] This represents within subject standard deviation multiplied by 2.77. The within subject standard deviation was calculated from the square root of the variance which represents half of the square of differences of visits 1 and 2 results. *Abbreviations*: R_5: resistance at oscillation frequency of 5 Hz; X_5: reactance at oscillation frequency of 5 Hz; l = litre; l/s: litres per second; kPa/l/s: kilo-Pascal per litre per second.

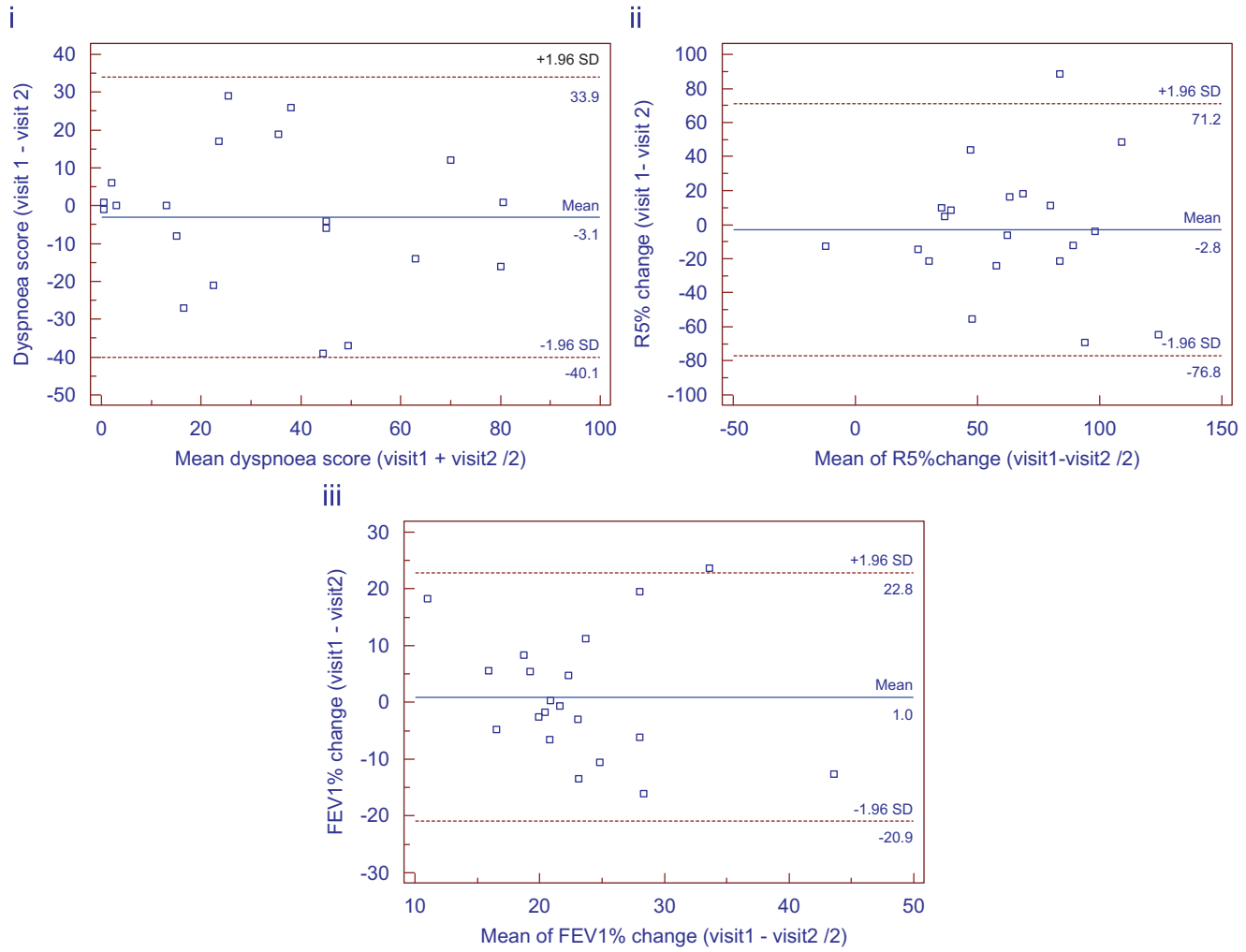

Figure 1 Repeatability of the two visits results using Bland–Altman plots. Comparison is made between post-challenge change in (i) dyspnoea scores, (ii) %R_5, and (iii) %FEV_1. Similar results were obtained for tightness, wheeze, X_5 and MEF_{50} scores (data not shown).

dyspnoea and tightness symptoms with both IOS and spirometry was similar and somewhat different from wheeze (Table 3). A possible explanation for such findings is a differing underlying pathophysiology. Dyspnoea and possibly chest tightness originate in complex and not yet fully understood mechanisms that include increased resistive work of breathing through activation of respiratory muscle, hyperinflation, and non-mechanical stimuli.[5,34] Wheeze on the other hand might be a true representation of the actual airway calibre and hence its significant correlation with spirometry.[20]

Our findings of close correlation between methacholine-induced dyspnoea and R_5 but not FEV_1, is consistent with earlier reports of increased sensitivity of the FOT over spirometry in subjects with either reactive airways disease or those exposed occupationally to toxic fumes or other inhalants.[11] Schmekel and Smith used inhalation of cold air as a bronchial challenge test in both asthmatics and healthy controls. Their results indicated that FOT was more able to discriminate between the two groups than spirometry with superior specificity and sensitivity (89% and 88% for R_5 and 88% and 73% for FEV_1, respectively).[21] IOS is somewhat different from the classical FOT. Hellinckx et al.[22] compared the two techniques and concluded that the two systems were similar but not identical in measurement of respiratory system *resistance* and *reactance*. More recent IOS-based studies continued to report similar findings of increased sensitivity of the oscillation technology. Kohlhaufl et al.[23] examined healthy non-smokers versus asymptomatic smokers, and demonstrated a three times higher post-methacholine challenge *reactance* values as compared to FEV_1 in the asymptomatic smokers group, which were attributed to possible underlying subclinical bronchiolitis. Skloot et al.[24] assessed ironworkers at the World Trade Centre disaster site, and reported that spirometry significantly underestimated the prevalence of lung function abnormalities in symptomatic subjects as compared with IOS.

The role of methacholine challenge testing in asthma diagnosis has been previously reviewed, and is largely seen to have high negative predictive value of more than 90% when the pre-test asthma probability is 30–70%.[19] Furthermore, most authors conclude a negative methacholine challenge will virtually rule out asthma if the subject was symptomatic in the 2 weeks prior to the test. However, it is clear that a significant proportion of asthmatics do not consistently reach this diagnostic gold standard (PC_{20}–FEV_1)

despite development of asthma symptoms during the challenge (e.g. chest tightness or dyspnoea).[2] Several studies have reported significant correlations between the changes in FOT measured R_{rs} and FEV_1 following induced bronchoconstriction[25–27] while others including this study showed no significant correlation.[22] Broeders et al. compared the FOT measured PC_{40}–R_6 with the PC_{20}–FEV_1 in stable asthmatics,[10] and showed that PC_{40}–R_6 was achieved at a significantly lower methacholine concentration than PC_{20}–FEV_1 and in shorter time span. Such discrepancy between FOT and spirometry is probably a reflection of differences in the conduct of their measurements. Maximal inspirations and forced expirations in spirometry require full patient cooperation, and repeated manoeuvres may fatigue the respiratory muscle. Previous studies also showed that repeated deep inspiration can induce bronchodilation particularly in asymptomatic asthmatics, which could influence the outcome of a bronchial provocation test.[28–32] IOS has the advantage of only requiring quiet breathing without the need for an initial deep inspiration. However, in our study, the deep inspiration required for spirometry may influence subsequent IOS as well as spirometric measurements during the challenge. Conducting a study that compares IOS-based methacholine challenge alone versus IOS and spirometry together may be useful in addressing this issue. Differences between FEV_1 and R_{rs} may also reflect differences in the various aspects of the pathophysiology of

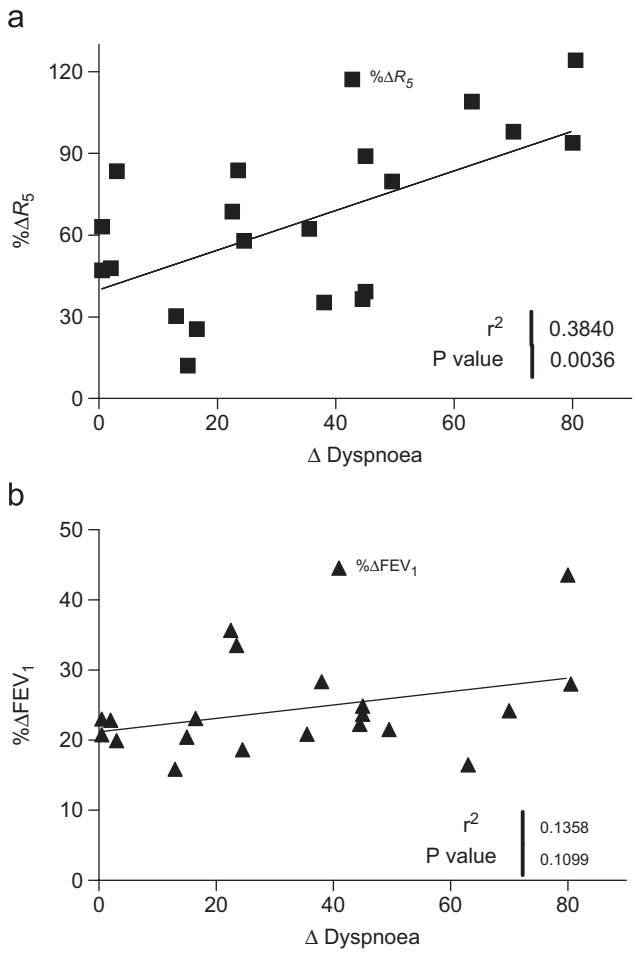

Figure 2 Linear regression analysis of post-methacholine challenge changes in dyspnoea scores (Δdyspnoea), on % change in R_5 (%ΔR_5) (Fig. 1a), and % change in FEV_1 (%ΔFEV_1) (Fig. 1b). A significant relationship is observed between Δ dyspnoea and %ΔR_5, but not with %ΔFEV_1. (For abbreviations, please refer to Tables 2 and 3 legends.)

Table 4 Results of stepwise forward linear regression of Δdyspnoea on %ΔR_5, %ΔX_5, %ΔFEV_1 and %ΔMEF_{50} (representing mean values of the percentage of difference between pre- and post-methacholine challenge for visits 1 and 2 combined).

Model	Regression coefficient	Standard error	*T*	*p*
Included variables				
Constant	3.5	1.0	0.35	0.73
%ΔR_5	−0.49	1.4	−3.5	0.003
Excluded variables				
%ΔX_5	−0.36		−1.7	NS
%ΔFEV_1	0.21		1.13	NS
%ΔMEF_{50}	0.13		0.65	NS

The sum of squares for %ΔR_5 is 4955.64/12320.2, $R^2 = 40\%$.

Table 3 Changes in symptom scores following challenge.

	ΔDyspnoea	ΔTightness	ΔWheeze	%ΔR_5	%ΔX_5	%ΔFEV_1	%ΔMEF_{50}
ΔDyspnoea	1.0	0.95**	0.80**	0.63**	0.60**	0.37	0.35
ΔTightness		1.0	0.86**	0.59**	0.51*	0.42	0.46
ΔWheeze			1.0	0.48*	0.62**	0.49*	0.46*
%ΔR_5				1.0	0.58**	0.28	0.37
%ΔX_5					1.0	0.45*	0.47*
%ΔFEV_1						1.0	0.75**
%ΔMEF_{50}							1.0

The dyspnoea, wheeze and tightness values represent mean change (Δ) from baseline following methacholine challenge, which is measured on 100 mm scale. The R_5, X_5, FEV_1 and MEF_{50} variables are represented as the mean % change (%Δ) from baseline following methacholine challenge. The Δ and %Δ values correspond to the mean of the combined values for visits 1 and 2. Correlations that reach statistical significance are marked in bold as (*$p<0.05$, **$p<0.01$, two tailed). In addition to Pearson's coefficient analysis, non-parametric Spearman's coefficient yielded very similar results.

airflow obstruction (e.g. small airway inflammation) that were not detected by FEV_1, but were correctly detected by R_{rs}. It may be argued therefore that R_{rs} could have a higher sensitivity and lower false negative rate than FEV_1 in asthma diagnosis in methacholine challenge setting. Conversely, the replacement of FEV_1 with R_{rs} in methacholine challenge tests may exaggerate the overlap of positive bronchial hyperresponsiveness between asthmatics and individuals who have rhinitis and no lung disease for example, thus reducing the test specificity and the positive predictive value for asthma. To be integrated in clinical use, IOS-based bronchial provocation testing will require further characterisation of its sensitivity and specificity in relation to FEV_1 in larger normal and asthmatic populations.

Studies on the reproducibility of oscillometry-based techniques indicated 5–15% intra-individual variability which is comparable to the variability of resistance values of other methods such as body plethysmography.[13] In this study, to confirm validity and repeatability of our results, subjects underwent two bronchial challenges 2–3 weeks apart. These showed close result repeatability between the two visits (Table 2, Figure 1). The IOS parameters (R_5 and X_5) showed similar correlation pattern in relation to asthma symptoms. However, in contrast to R_5, X_5 demonstrated significant correlation with FEV_1 and MEF_{50}. This finding is consistent with previous studies that demonstrated more negative (decreased) reactance "X_{rs}" as airways obstruction increases, which appeared to correlate more strongly with FEV_1 and plethysmographic airway resistance (R_{aw}) than did R_{rs}.[11] The X_{rs} of the respiratory system represents the spectral relationship between the pressure component out of phase with flow and the flow. It is thought to reflect the inertive and elastic properties of the lungs rather than a measure of airway obstruction, which is intriguing considering its reported correlation with other measures of airway resistance. Johnson et al. recently reported that X_{rs} could predict transpulmonary resistance (measured by oesophageal manometry) more accurately than can the R_{rs}.[33] Increased susceptibility of R_{rs}, as opposed to X_{rs}, to upper airway wall shunting was put forward as a possible explanation. However, in our multiple regression model (Table 3), R_5 was the only significant variable that explained dyspnoea, which further emphasised its role as a candidate measurement in bronchial provocation tests.

It is not yet clear which cut-off value for R_5 would correspond to bronchial hyperresponsiveness. Previous studies suggested that threshold values up to a 47% increase in R_{5-10} are associated with a higher number of positive responders than is the case of PC_{20}–FEV_1, while other studies estimated this threshold value lies between a 65% and 90% increase in R_{5-10}.[15] Our study design does not allow the estimation of such a threshold, although in this sample of stable asthmatics we observed a mean post challenge change in R_5 of 61.7% (SD = 37.4) in visit 1 and 64.5% (SD = 38.4) in visit 2. R_{rs} at higher frequency (R_{20}) have also been analysed in this study. We observed no significant correlation between asthma symptoms and R_{20} (the Pearson correlation of Δdyspnoea to $\%\Delta R_{20} = 0.064$, $p = 0.79$). R_{20} represents the upper and central resistance measure and its relative value to R_5 rather than its absolute value which has been shown to be useful in determining clinical entities such as upper airway dysfunction (R_{20} larger than R_5).

In conclusion, we have shown a significant correlation between IOS-based measurements of respiratory resistance and methacholine-induced asthma symptoms. In contrast, the correlation of such symptoms with spirometric-based measurements was either non-significant or weak. These data therefore support the notion of IOS superiority to spirometry in assessment of bronchial responsiveness. The ease of IOS data acquisition and its superior sensitivity to spirometry in methacholine challenge would argue for a further study in a large population to establish the sensitivity and specificity of IOS-based methacholine challenges in asthma diagnosis and monitoring. This would also be important in the understanding of symptoms such as chest tightness of which patients frequently complain but are often dismissed as they bear little consistent relationship to indices of conventional lung function assessment.

Conflict of interest

There is no conflict of interest to declare. The work reported in this study is funded by an academic grant from British Oxygen Company. However, the latter has no influence on the conduction of the study or the analysis of its results.

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