

Comparison of bronchodilator response in patients with asthma and healthy subjects using spirometry and oscillometry

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Background: Impulse oscillometry (IOS) is an effort-independent and patient-friendly pulmonary function technique, but limited data are available that correlate the bronchodilator response using spirometry and IOS in adult asthmatic and healthy subjects.

Objective: To compare spirometry and IOS in ongoing bronchodilator response.

Methods: The study was a prospective evaluation of patients with asthma and healthy subjects attending screening at a research unit in a university teaching hospital. Reversibility testing was carried out using standardized American Thoracic Society/European Respiratory Society (ATS/ERS) criteria after administering 400 μ g salbutamol by AccuhalerTM. Impulse oscillometry measurements (resistance at 5 Hz [R5], resistance at 20 Hz [R20], reactance at 5 Hz [X5]) and spirometry (forced expiratory volume in 1 second [FEV₁], forced vital capacity [FVC], forced expiratory flow from 25% to 75% of vital capacity [FEF₂₅₋₇₅]) were recorded pre and postbronchodilator.

Results: Ninety-five asthmatic and 61 healthy subjects underwent screening. Mean percent (standard error of the mean [SEM]) baseline prebronchodilator FEV₁ was 83.99 (2.23) for patients with asthma, and 99.25 (1.72) for healthy subjects. Baseline percent predicted IOS indices in the group with asthma were 162.22 (7.5) for R5; 154.73 (4.71) for R20; and 441.72 (173.86) for X5. In healthy volunteers, corresponding values were 111.01 (3.96), 127.75 (4.12), and -229.80 (125.75). R5 was the only IOS measure that showed correlation with spirometry (FEV₁) in both groups. The mean percent (SEM) predicted postbronchodilator change in FEV₁ and R5 in patients with asthma was 6.35 (0.65) and -33.78 (4.43); correspondingly in healthy subjects it was 2.24 (0.32) and -14.91 (2.48). A negative correlation was demonstrated ($r = -0.40$, $P < .001$ between the 2 indices in patients with asthma. Linear regression modeling demonstrated that 1 unit change in %FEV₁ corresponds to a 2.5% change in %R5.

Conclusions: Low-frequency IOS as R5 and spirometry as FEV₁ correlate in patients with asthma and healthy subjects, with changes that can be predicted by linear regression.

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INTRODUCTION

The assessment of bronchodilator response is conventionally expressed as percentage of predicted change in spirometric indices such as forced expiratory volume in 1 second (FEV₁) or forced vital capacity (FVC),¹ but it also may be expressed as percent and absolute changes from baseline. The American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines consider a greater than 12% and 200-mL change from baseline in FEV₁ as a significant bronchodilator response during a single testing session.² However, the reliability of spirometric maneuvers is dependent on active patient cooperation and their ability to perform the forced maneuvers to established ERS/ATS quality control standards.³ This can

often be an issue in pediatric and certain adult subsets, including the elderly.

Impulse oscillometry (IOS) is a sensitive rapid effort independent technique for real-time assessment of lung function that requires minimal patient cooperation.⁴⁻⁶ It incorporates the application of forced aperiodic small external pressure impulses that are superimposed on spontaneous breathing using an external impulse generator.^{7,8} It avoids the common pitfalls associated with conventional spirometry techniques, namely, the need for forced maximal inhalation and expiratory breathing maneuvers that influence airway caliber.^{9,10}

Despite the putative advantages of using the IOS system, few data are available on the use of IOS in reversibility testing in the adult asthma population, or on how it compares to traditional reversibility testing using spirometry. We have therefore carried out an evaluation to compare bronchodilator responsiveness after 400 μ g Salbutamol in patients with asthma and healthy volunteers, using spirometry and IOS indices.

METHODS

Subjects

The subjects were all patients with asthma and healthy volunteers between the ages of 18 and 65 years who were attending the asthma and allergy research group center at the

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Table 1. Baseline Lung Function Measurements and Demographics in Patients with Asthma and Healthy Volunteers

	Patients with asthma <i>N</i> = 82	Healthy volunteers <i>n</i> = 61	Difference, 95% CI, <i>P</i>
Male (female)	28 (54)	27 (34)	—
Age (yr) ^a	48.7 (16.51)	28.2 (10.13)	20.5 (15.8–25.2), <i>P</i> < .001
FEV ₁ %predicted ^b	83.99 (2.23)	99.25 (1.72)	15.25 (9.34–21.17), <i>P</i> < .001
FVC %predicted ^b	95.01 (2.15)	99.12 (1.67)	4.11 (–1.65–9.87), <i>P</i> = .16
R5 %predicted ^b	162.22 (7.5)	111.01 (3.96)	51.12 (32.29–69.95), <i>P</i> < .001
R20 %predicted ^b	154.73 (4.71)	127.75 (4.12)	26.97 (39.84–14.10), <i>P</i> < .001
X5 %predicted ^b	441.72 (173.86)	–229.80 (125.75)	671.53 (1,129.13–213.93), <i>P</i> = .004
FE _{NO} (ppb) ^c	25.46 (1.09)	16.11 (1.08)	1.58 ^d (1.23–2.01), <i>P</i> < .001
ICS (μg) ^e	800 (0–1,000)	—	—

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; R5, resistance at 5 Hz; R20, resistance at 20 Hz; X5, reactance at 5 Hz; FE_{NO}, fractional exhaled nitric oxide; ICS, inhaled corticosteroids.

^a Mean (SD).

^b Mean (SEM).

^c Geometric mean (SEGM).

^d Geometric mean fold difference.

^e Median (interquartile range).

University of Dundee for routine screening between February 2006 and January 2007. Because this was a study of anonymous data from subjects who were attending for routine screening tests and were not enrolled in a clinical trial, the Tayside Committee for Medical Research and Ethics allowed us to proceed after obtaining Caldicott guardian approval, which was duly obtained.

Study Design

This was a single-center prospective evaluation of subjects attending the asthma and allergy research group. The routine screening program comprised two visits separated by a minimum of 24 hours. All volunteers who expressed a desire to participate in clinical trials completed a previsit screening history questionnaire that included details of full medical history and a list of current medications. At the first screening visit, the medical history questionnaire was reviewed, a full physical examination was performed, and a series of preliminary investigations, including skin prick testing, assessment of exhaled nitric oxide, followed by IOS, spirometry, and bronchodilator response, were performed. They were subsequently invited to attend the second screening visit, during which methacholine challenge testing was performed. Baseline measurements were recorded for spirometry (FEV₁, FVC) and IOS (resistance at 5 Hz [R5], resistance at 20 Hz [R20], reactance at 5 Hz [X5]) as a percentage of predicted values. The IOS indices of R5, R20, and X5 refer to airway resistance at 5 Hz, 20 Hz, and reactance at 5 Hz, respectively. Fraction of exhaled nitric oxide (FE_{NO}) was recorded in parts per billion. Inhaled corticosteroid dose was recorded for volunteers with asthma.

The volunteers with asthma were asked to withhold their short-acting bronchodilator for at least 6 hours, long-acting bronchodilator for at least 48 hours, and theophylline for 48 hours before attending the department for testing. Patients taking inhaled corticosteroids were instructed to continue using their inhalers as usual. The first measurements to be taken were of

exhaled nitric oxide using an Aerocrine NIOX machine, using ATS/ERS guidelines.¹¹ Three consecutive technically satisfactory recordings were taken. Subsequently, the IOS measurements were performed followed by spirometry.

Impulse Oscillometry System

The impulse oscillometry system is the commercially available form of the forced oscillation technique and is based on

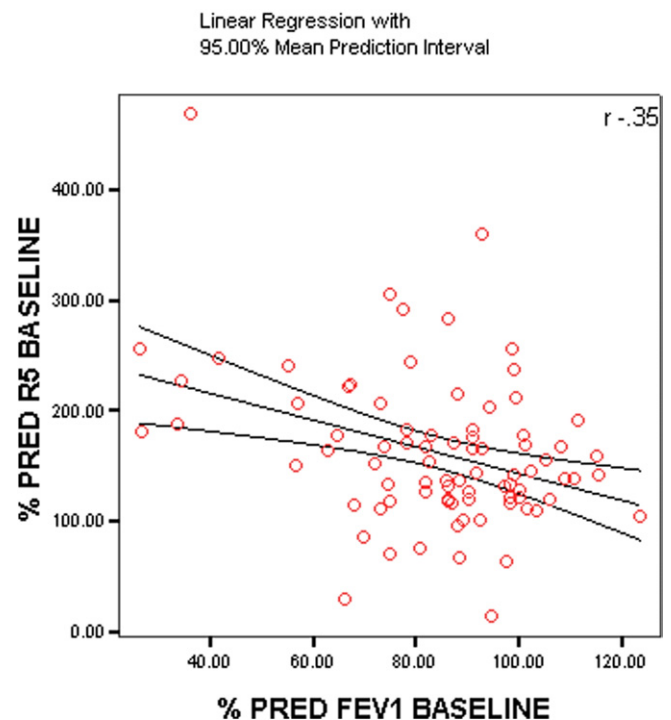


Figure 1. Correlation between percent predicted FEV₁ and R5 at baseline in patients with asthma.

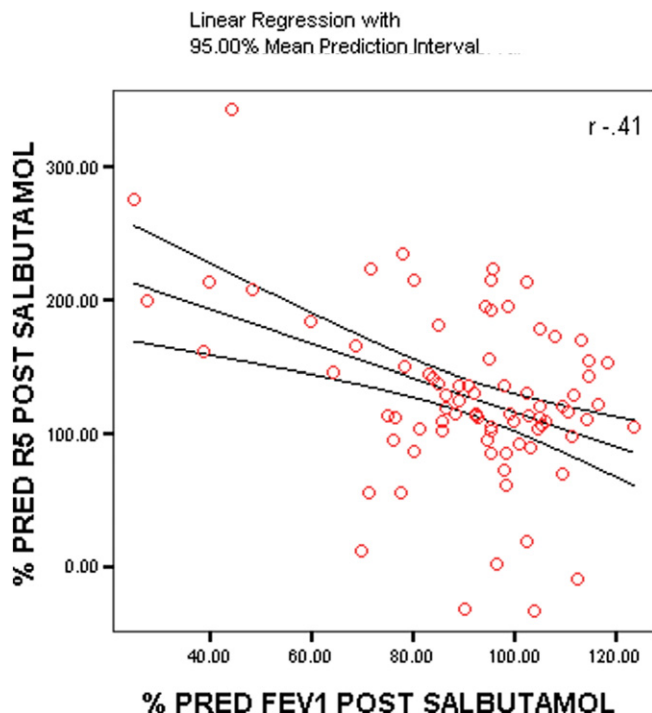


Figure 2. Correlation between percent predicted FEV₁ and R5 post bronchodilator in patients with asthma.

the extrapolation of the principle of resistance being equal to pressure/flow.^{12,13} In the case of IOS, the oscillometric resistance is the ratio of impulse pressure to impulse flow after elimination of the superimposed breathing fractions. The system works by sending sharp peak impulses with a maximum duration of 45-ms pulses of pressure, using a loud-speaker into the patient's airways as the patient breathes normally through a mouthpiece.¹² By penetrating the airways, these pressure impulses generate corresponding flow excursions. Simultaneously recorded impulse pressure and flow are analyzed with regard to their frequency content, using fast Fourier transformation model to provide information on airway resistance, reactance, and impedance, which are measured and analyzed continuously with respect to pressure, flow, and frequency, using a fast Fourier transformation model to provide information on airway resistance, reactance, and impedance. The frequency spectrum of the impulse also determines depth of penetration, with low frequencies (5 Hz) being able to penetrate the entirety of the lungs and the higher frequency (20 Hz) penetrating only the central airways, thus permitting assessment of differential total, central, and peripheral airway resistance. Furthermore, because an impulse encompasses an entire frequency band, it provides a source for a continuous spectrum of frequencies, allowing improvement of the noise-to-signal ratio^{12,14} by discriminating test frequencies from breathing frequencies.

Impulse oscillometry was performed using the Jaeger MasterScreen-IOS (Carefusion Technologies, San Diego, Cal-

ifornia), using a standardized protocol based on manufacturer instructions. Subjects were seated in front of the machine with their neck slightly extended and their lips sealed tightly around the mouthpiece, and while wearing a nose-clip and pressing on their cheeks to prevent the upper airway shunt that can occur because of the loss of impulse pressure through the cheeks. They were asked to breathe normally, and their breathing pattern was observed in real time on the screen of the machine. Once a steady pattern of tidal breathing was established, data acquisition was initiated for 30 seconds. This was repeated three times, and quality of measurements was ensured by visual inspection of the waveforms and evaluation of the coherence spectrum.

Spirometry

Spirometry measurements were made in triplicate using the MicroMedical Super Spiro (Carefusion 232 Ltd, Kent, United Kingdom) with a Clement Clarke international one-way mouthpiece as per standardized ATS/ERS protocol (Clement Clarke International Ltd, Harlow, United Kingdom). Subjects were then given 400 µg salbutamol via an Accuhaler device, using standard ERS/ATS guidelines.³ Fifteen minutes after administration of the salbutamol, the IOS and spirometry measurements were repeated. These, together with the other screening data, were recorded and subsequently analyzed.

Data and Statistical Analysis

Statistical analysis was carried out using SPSS version 13.0 (SPSS Inc, Chicago, Illinois. Data were assessed for normality before analysis. The FE_{NO} and methacholine PC₂₀ measurements

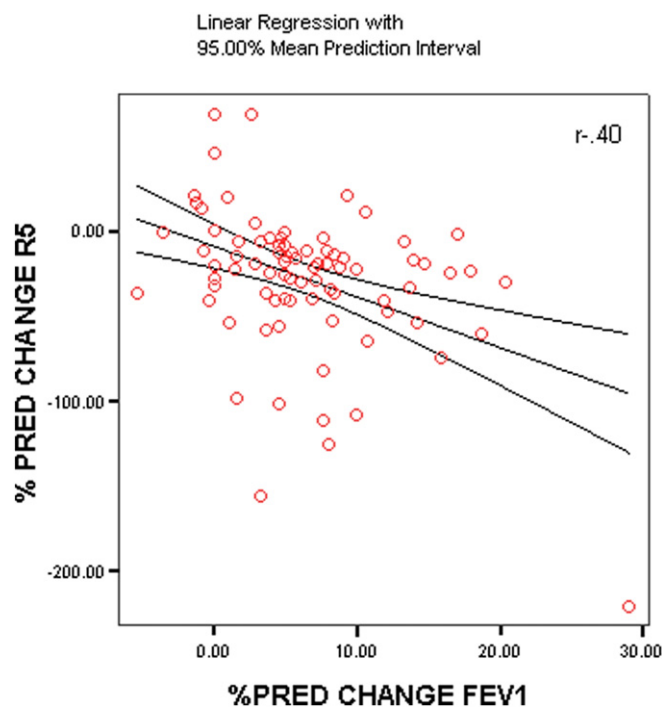


Figure 3. Correlation of the bronchodilator response measured as a percentage of predicted change in FEV₁ and R5 in patients with asthma.

Table 2. Bronchodilator Response % Predicted Change in Patients with Asthma and Healthy Volunteers

Lung Function variable	Asthmatics	Healthy Volunteers	Difference ^b
FEV ₁ ^a	6.35 (.65)	2.24 (.32)	4.10 (5.70 to 2.50), $P < .001$
FVC ^a	2.16 (.79)	-.25 (.40)	2.41 (4.36 to .46), $P = .01$
R5 ^a	-33.78 (4.43)	-14.91 (2.48)	18.86 (7.85 to 29.88), $P = .001$
R20 ^a	-19.96 (3.81)	-15.68 (2.64)	4.27 (-5.57 to 14.12), $P = .39$
X5 ^a	-72.93 (88.73)	40.09 (65.64)	113 (-121.64 to 347.71), $P = .34$

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; R5, resistance at 5 Hz; R20, resistance at 20 Hz; X5, reactance at 5 Hz. Data presented as % predicted values.

^a Mean (SEM).

^b Mean differences, 95% CI, P value.

were non-normally distributed and therefore log transformed before analysis and are expressed as geometric mean with the corresponding standard error. Analyses of results for the patients with asthma and for the healthy volunteers were done using paired t -test. For comparisons between healthy volunteers and patients with asthma, independent sample t -tests were used. Within-test repeatability of IOS measurements was analyzed in terms of coefficient of variation (CV%), defined as the residual mean square of the 3 baseline readings, expressed as percentage of the mean (analysis of variance). Correlations between percent predicted FEV₁ and R5 values were calculated using linear regression. A linear regression model was constructed to predict the outcome of unit change in FEV₁ and R5 by first identifying the overall fit of the model and by analyzing the standardized beta coefficient. $P < .05$ was considered significant.

RESULTS

A total of 95 subjects with asthma and 61 healthy volunteers were screened, and of the 95 with asthma 13 subjects had incomplete data recorded in the screening sheets and were excluded from the analysis. Sixteen of the subjects with asthma were current smokers.

Demographics

Details of the remaining 82 patients with asthma and 61 healthy volunteers are given in Table 1. Of the group with asthma, 35.3% were male, and 64.7% were female. The mean age was 48.7 years (standard deviation, 16.5). Among the

healthy volunteers, 44.3% were male and 55.7% female; mean age, 28.2 years (standard deviation, 10.3).

Baseline Lung Function Measurements (Table 2)

Spirometry. In patients with asthma, the mean FEV₁ was 83.99% predicted (standard error of the mean [SEM], 2.23); In the healthy volunteers, FEV₁ was 99.25% (SEM, 1.72). Forced vital capacity was 95.01% of predicted (SEM, 2.15) in the group with asthma and 99.12% predicted (SEM, 1.67) in the healthy volunteers.

IOS Readings. The baseline before salbutamol within-test variance of IOS % R5 measurements (in terms of coefficient of variation) was 4.29% in patients with asthma, and after salbutamol, 4.51%. In healthy volunteers, the coefficient of variation for % R5 was 2.90% and 2.91% for pre and post salbutamol, respectively.

The baseline R5 was 162.22% predicted (SEM, 7.5) in the patients with asthma and 111.01% predicted (SEM, 3.96) in the healthy volunteers, with a difference of 51.12 (CI 32.29–69.95, $P < .001$). R20 was 154.73% predicted for patients with asthma (SEM, 4.71) and 127.75% predicted for healthy volunteers (SEM, 4.12), with a difference of 26.97 (CI 39.84–14.10; $P < .001$). X5 was 441.72% predicted in patients with asthma (SEM, 173.86) and -229.80% predicted in the healthy volunteers (SEM, 125.75), with a difference of 671.53 (95% confidence interval [CI], 1129.13–213.93, $P = .004$).

Table 3. Lung Function Measurements Pre and Post Bronchodilator in Patients with Asthma and Healthy Volunteers

Asthma				Healthy volunteers		
Baseline	Post Salbutamol	Difference ^b		Baseline	Post Salbutamol	Difference ^b
FEV ₁ % ^a	83.99 (2.23)	90.34 (2.22)	6.34 (7.64–5.04) <i>P</i> < .001	99.25 (1.72)	101.50 (1.74)	2.25 (2.90–1.59), <i>P</i> < .001
FVC % ^a	95.01 (2.15)	97.17 (2.15)	2.15 (3.74–.57) <i>P</i> = .008	99.12 (1.67)	98.87 (1.70)	–.25 (.55–1.05), <i>P</i> = .53
R5 % ^a	162.22 (7.5)	128.35 (6.97)	–33 (–24.96–42.59) <i>P</i> < .001	111.01 (3.96)	96.09 (3.44)	–14.91 (–9.93–19.88), <i>P</i> < .001
R20 % ^a	154.73 (4.71)	134.66 (5.28)	–20.06 (–12.37–27.75) <i>P</i> < .001	127.75 (4.12)	112.07 (3.98)	–15.68 (–10.39–20.97), <i>P</i> < .001
X5 % ^a	441.72 (173.86)	368.79 (131.19)	–72.93 (103.76–249.63) <i>P</i> = .41	–229.80 (125.75)	–189.70 (103.78)	40.09 (171.69–91.44), <i>P</i> = .54

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; R5, resistance at 5 Hz; R20, resistance at 20 Hz; X5, reactance at 5 Hz.

^a Mean (SEM).

^b Mean difference, 95% CI, P .

FE_{NO} at Baseline. The geometric mean of 25.46 parts per billion (ppb) in the group with asthma (standard error of the geometric mean [SEGM], 1.09), compared with 16.11 ppb in the healthy volunteers (SEGM, 1.08). The geometric mean fold difference was 1.58 (CI 1.23–2.01, $P < .001$).

Methacholine PC₂₀ at Baseline. In subjects who attended the second screening visit ($n = 41$), the geometric mean PC₂₀ was 0.80 mg/mL, with an SEGM of 0.15 in the subgroup with asthma.

Inhaled Corticosteroid Dose. Sixty-six percent of the patients with asthma were being treated with inhaled corticosteroids. The median inhaled corticosteroid dose in the volunteers with asthma was 800 μ g, with an interquartile range of 0 to 1,000 μ g. Of asthmatic subjects, 64% were atopic.

Bronchodilator Response (Tables 2 and 3)

Spirometry. The mean change in FEV₁ was 6.35% in patients with asthma (SEM, 0.65) and 2.24% in healthy volunteers (SEM, 0.32), with a mean difference between the groups of 4.1% (95% CI 5.70–2.50, $P < .001$). The mean change in FVC was 2.16% in patients with asthma (SEM, 0.79) and -0.25 in healthy volunteers (SEM, 0.40), with a mean difference between the groups of 2.41 (95% CI 4.36–0.46, $P = .01$).

Impulse Oscillometry. The mean change in R5 was -33.78% in patients with asthma (SEM, 4.43) and -14.91% in healthy volunteers (SEM, 2.48). The difference between the groups was 18.86 (95% CI 7.85–29.88, $p = .01$). For R20, the mean change was -19.96% for patients with asthma (SEM, 3.81) and -15.68% for healthy volunteers (SEM, 2.64); the difference between the groups was 4.27 (95% CI, -5.57 – 14.12 , $P = .39$). Mean change in X5 was -72.93% for patients with asthma (SEM, 88.73) and 40.09% for healthy volunteers (SEM, 65.64); the difference was 113 (95% CI, -121.64 – 347.71 , $P = .34$).

Correlation (Figs 1-3)

A negative correlation between percent predicted FEV₁ and R5 was noted at baseline and after bronchodilator, with an r value of -0.35 , $P = .001$ at baseline and r value of -0.4 , $P < .001$ for the bronchodilator response in patients with asthma. Using a linear regression prediction model, one could estimate that a 1% change in FEV₁ would equate to a 2.5% change in R5. In a subgroup of 31 patients with asthma, in which the forced expiratory flow between 25% and 75% of FVC (FEF₂₅₋₇₅) values were recorded, a negative correlation was found between % predicted FEF₂₅₋₇₅ and % predicted R5, which was not statistically significant, $r = -0.32$, $P = .07$; for bronchodilator response, significant negative correlation was found between FEF₂₅₋₇₅ and R5; $r = -.47$, $P = .008$.

DISCUSSION

The results of the current study have shown that IOS resistance measurements at 5Hz (R5) and 20Hz (R20) both demonstrated significant response to bronchodilator testing in patients with asthma and healthy volunteers. A statistically significant but weak negative correlation between R5 and

FEV₁ was observed as in previous pediatric studies,¹⁵ and significant correlation was observed between R5 and FEF₂₅₋₇₅ for bronchodilator response in the subgroup with asthma.

Impulse oscillometry system resistance measurements of R5 are more sensitive than conventional spirometric indices and have been demonstrated to have a discriminating ability for bronchodilator responsiveness second only to body plethysmography-associated specific airway resistance measurements.^{5,6} In this regard, one must recognize that IOS measurements are less variable than plethysmography measurements^{6,16,17} and although spirometric indices of FEV₁ are more repeatable, IOS measurements are more acceptable to patients, because they are completely effort independent and eliminate the need to be enclosed within a box and carry out panting maneuvers. In our study, the within-test variability of IOS resistance measurements percent predicted R5 was slightly higher in patients with asthma as compared with healthy volunteers: 4.3% vs 2.9%. The within-test repeatability of the IOS resistance measurements in our mild adult population with asthma were comparable to results obtained in pediatric subjects: 4.3% vs 4.1% for R5¹⁵ and less than the 6% obtained in a much smaller adult study.⁶ The low variability of R5 therefore makes it an attractive sensitive surrogate measure for clinical comparisons in a range of clinical settings, including post lung transplant patients and therapeutic clinical trials.

Impulse oscillometry measurements measure resistive and reactive components of respiratory impedance, whereas spirometry determines volume or flow generated by the individual over time. The IOS resistance measurements (R) include proximal and distal airways, lung tissue, and chest wall resistance, and evidence of frequency dependence is seen with increasing distal airflow obstruction. R5 values of less than 150% predicted is considered to be within normal limits, and R5 values increase above normal limits with proximal or distal airway obstruction.¹² Although IOS resistance and spirometry measurements correlate, the agreement between the 2 measurements is less reliable given the inherent differences. This is perhaps unsurprising, because they are measuring different aspects of lung function. The FEV₁ is limited in its ability to measure predominantly large airway caliber in an effort-dependent manner as compared with IOS, which represents a tidal breathing analysis of the resting situation in a given patient. As expected, after the administration of a bronchodilator, we were able to demonstrate that FEV₁ will increase, and R5, representing airway resistance, will decrease in patients with asthma and healthy volunteers. The correlation co-efficients obtained from FEV₁ and R5 in patients with asthma showed statistically significant negative correlations for baseline, post salbutamol, and bronchodilator response, confirming the predicted outcome. Various cutoffs have been suggested for expressing IOS bronchodilator responsiveness.^{5,18} Hellinckx and colleagues¹⁸ suggested a cutoff level of 40% delta percentage of initial R5; however, Neilson⁵ and colleagues reported cutoff values of delta R5 percentage of initial of 29% and 27% when expressed as delta percent predicted. Similarly Marotta et al,¹⁹ in their comparative bronchodilator responsiveness evaluation in young children with asthma, reported delta changes of 20 to

25% R5 as being a good discriminator of bronchodilator responsiveness. However, one must recognize that our study was a priori not designed to compare sensitivity or specificity of specific cutoffs of bronchodilator responsiveness in terms of delta percent predicted R5. Our sample size permitted us to reliably use a linear regression prediction model to determine that a 1% change in percent FEV₁ would equate to a 2.5% change in percent R5. This will help clinicians to relate to and comprehend changes in percent R5 more easily. We find the use of percentage predicted changes in X5 as a means of measuring bronchodilator responsiveness unsuitable and potentially misleading in view of the extremely high magnitude of percentage changes, and absolute values of changes in X5 would be a preferable outcome measure for reporting in future clinical trials.

The IOS as a clinical resource has untapped potential that has been explored predominantly in children. Its ease of use, effort independence, and portability potentially allow use in the elderly and in patients unable to comply with forced maneuvers. Our current data included subjects between the ages of 18 and 65 years, and therefore the applicability or extrapolation of our data to the very young or the elderly cannot be validated without additional studies in the aforementioned groups. Finally, given its increased sensitivity as compared with FEV₁, IOS may be a more reliable objective measurement for identifying bronchiolitis obliterans syndrome in post lung transplant patients, who, particularly in the early posttransplantation period, have difficulty carrying out forced maneuvers. In this regard, researchers and clinicians would be advised to consider evaluation of the smaller airways function by monitoring oscillometric changes in resonant frequency and X5 instead of R5.

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