

Usefulness of impulse oscillometry for the assessment of airway hyperresponsiveness in mild-to-moderate adult asthma

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ABSTRACT

Background: Impulse oscillometry (IOS) is a novel method of assessing airway resistance. IOS is rarely used in assessing airway resistance after bronchoprovocation in adult asthma.

Objective: To ascertain the degree of change in IOS measurements seen in patients with asthma undergoing bronchial challenge testing.

Methods: Patients 18 to 65 years old with mild to moderate asthma, forced expiratory volume in 1 second (FEV₁) greater than 80% predicted, and diurnal FEV₁ variation less than 30% and taking inhaled corticosteroid ($\leq 1,000$ μ g/day of beclomethasone dipropionate equivalent dose) were recruited. Sequential spirometry and IOS results were measured during bronchial challenge testing to inhaled methacholine and histamine.

Results: The magnitude of percentage of change demonstrated in total airway resistance at 5 Hz was greater than that observed for FEV₁ in the 2 bronchial challenge tests. For example, at a methacholine provocation concentration that caused a decrease in FEV₁ of 20%, a 43.5% change (95% confidence interval 29.4–57.5) was seen in total airway resistance at 5 Hz as measured by IOS compared with a 23.3% change (95% confidence interval 18.7–27.9) in FEV₁. The magnitude of change seen with other IOS outcomes, including peripheral airway resistance, area under the curve, and resonant frequency, also was greater compared with spirometry.

Conclusion: The potential application of IOS in the assessment of airway hyperresponsiveness in adult asthma has been demonstrated. Further population studies are required.

Trial Registration: www.clinicaltrials.gov (NCT01074853).

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Introduction

The measurement of airway hyperresponsiveness (AHR) is integral within the assessment of asthma. Historically, conventional spirometry has been used to quantify the degree of airway obstruction seen after the inhalation of bronchoprovocation agents such as methacholine or histamine.¹ Impulse oscillometry (IOS) is a novel effort-independent method of assessing airway resistance by the use of small-amplitude sound waves being superimposed on normal breathing cycles.² IOS provides an alternative technique to assess changes in airway tone and has been shown to be sensitive to measuring bronchodilatation to salbutamol and ipratropium within asthma and chronic obstructive pulmonary disease populations.^{3–5} Within their unit, the authors have found IOS to be a

more sensitive marker than spirometry for bronchodilation to salbutamol and bronchoconstriction to propranolol.^{5,6} Furthermore, owing to the relative simplicity of the technique, within pediatric populations, IOS has been shown to be a useful alternative to spirometry.⁷ The usefulness of IOS in children has been well demonstrated and has even shown evidence of AHR in the absence of significant changes in spirometry.⁸ This has allowed IOS parameters to be investigated as potential surrogate markers of AHR instead of spirometry in children.⁹

Guidelines incorporate a standardized decrease in forced expiratory volume in 1 second (FEV₁) of 20% after bronchial provocation (PC₂₀) as evidence of AHR.¹ Although IOS provides an alternative means of assessing airway tone after bronchial challenge testing, currently there are no defined criteria as to what a positive bronchial challenge test result would be when using IOS instead of spirometry in adult populations. The purpose of this study was to ascertain the degree of change in IOS measurements seen in patients with asthma undergoing bronchial challenge testing. This would aid in the development of a standardized IOS reference value for potential use in clinical trials.

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Table 1
Participant demographics

Subject/Sex	Age (y)	FEV ₁ %	FEV ₁ /FVC ratio	Methacholine PC ₂₀ (mg/mL)	BDP equivalent daily dose (μg)	Concurrent Medications
1/F	21	92	0.78	0.92	400	L, A, NS
2/F	64	99	0.71	2.48	400	L, LT, NS
3/F	31	85	0.75	0.99	500	A, LT
4/M	48	85	0.68	2.0	500	L, LT
5/F	65	103	0.69	0.71	200	—
6/M	29	98	0.71	1.36	100	—
7/M	57	106	0.81	3.45	1,000	NS
8/M	20	91	0.76	3.71	400	—
9/F	19	91	0.83	0.67	400	A
10/M	19	90	0.85	1.73	200	A
11/F	25	91	0.85	2.4	200	A
12/F	50	88	0.67	1.13	400	A, NS
13/M	57	88	0.76	2.19	200	A, NS
14/F	22	102	0.82	0.67	800	—
15/M	35	95	0.83	5.42	800	L, NS
16/F	46	91	0.72	0.31	1,000	L
17/F	21	85	0.75	3.31	200	—
18/M	25	86	0.76	0.1	200	L, A
Mean (SEM)	36 (4)	93 (2)	0.76 (0.01)	1.32 (0.81–2.15) ^a	440 (66)	

Abbreviations: A, antihistamine; BDP, budesonide; F, female; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; L, long-acting β -agonist; LT, leukotriene receptor antagonist; M, male; NS, nasal spray; PC₂₀, provocation concentration that causes a decrease in forced expiratory volume in 1 second of 20%.

^aData displayed as geometric mean (95% confidence interval). Data are presented as percentage predicted for age, gender, and race.

Methods

A post hoc analysis of a double-blinded, randomized, placebo-controlled trial of propranolol in patients with mild to moderate asthma was performed.¹⁰ The Tayside medical research ethics committee (Dundee, Scotland) gave approval before commencement of the trial (10/S0501/22). The study was registered with <http://www.clinicaltrials.gov> (NCT01074853) and all participants gave written informed consent.

Patients 18 to 65 years old with mild to moderate asthma, FEV₁ greater than 80% predicted, and diurnal FEV₁ variation less than 30% and taking inhaled corticosteroid ($\leq 1,000$ μg/day of beclomethasone dipropionate equivalent dose) were recruited. Participants were required to demonstrate AHR to a methacholine bronchial challenge at a PC₂₀ lower than 8 mg/mL. All participants were nonsmokers and free of an asthma exacerbation within the past 6 months. The Asthma Control Questionnaire (ACQ) was performed at baseline.

At the end of each study period (including the placebo limb) before crossover, each participant underwent a methacholine and a histamine bronchial challenge test. Bronchial challenge testing from the placebo limb was used in this analysis. Sequential IOS and

spirometry results were measured during bronchial challenge testing, with IOS being performed first.

Spirometry and IOS were performed in accordance with published guidelines.^{2,11} Participants supported their cheeks while impulses were applied during 30 seconds of tidal breathing. This maneuver allows airway resistance and reactance to be determined in large and small airways depending on the frequency. All measurements were performed in triplicate and means were taken. IOS measurements determine the degree of total airway resistance at 5 Hz (R5), peripheral airway resistance (R5 minus airway resistance at 20 Hz [R20]), and reactance (ie, lung compliance) as area under the curve and resonant frequency. For bronchial challenge testing, methacholine was made up into doubling dilutions with concentrations ranging from 0.03 to 32 mg/mL. Histamine was made up into doubling dilutions with concentrations ranging from 0.3125 to 40 mg/mL. A SuperSpiro spirometer (Micro Medical, Basingstoke, United Kingdom) and an IOS Jaeger Masterscreen (Wurzburg, Germany) were used.

Data were analyzed for normality using Shapiro-Wilk tests and boxplots. Values before and after the bronchial challenge were calculated and compared using paired Student *t* tests for

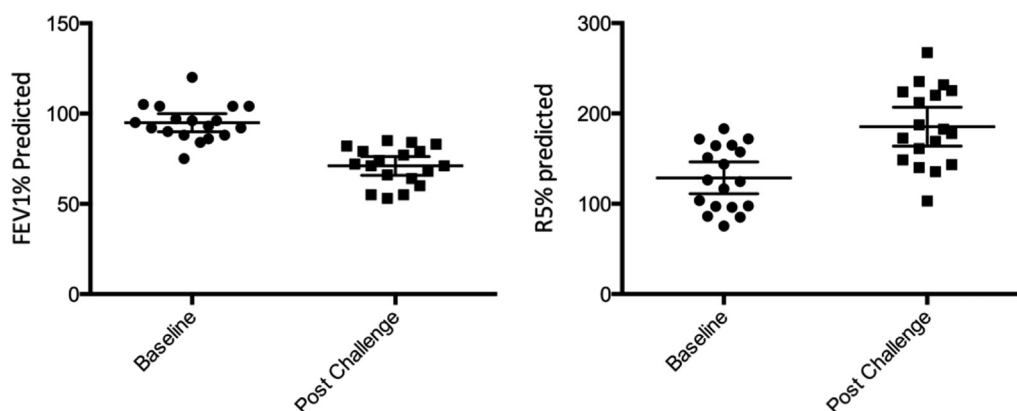


Figure 1. Percentage of predicted values before and after the methacholine bronchial challenge for forced expiratory volume in 1 second (FEV₁%) and total airway resistance at 5 Hz (R5%).

Table 2
Spirometry and impulse oscillometry

Outcome	Methacholine challenge		Mean percentage of change (95% CI)	Histamine challenge		Mean percentage of change (95% CI)
	Mean difference (95% CI)	<i>P</i> value		Mean difference (95% CI)	<i>P</i> value	
Spirometry						
FEV ₁ (L)	0.72 (0.54–0.9)	<.001	23.3 (18.7–27.9)	0.75 (0.6–0.91)	<.001	25.9 (21.0–30.8)
FEF _{25%–75%} (L/s)	0.84 (0.63–1.05)	<.001	32.8 (28.5–37.2)	0.91 (0.7–1.13)	<.001	37.8 (30.7–45.0)
FVC (L)	0.55 (0.39–0.71)	<.001	14.4 (10.6–18.1)	0.65 (0.54–0.76)	<.001	17.7 (13.9–20.4)
Impulse oscillometry						
Airway resistance						
R5 (kPa × L/s)	0.16 (0.12–0.21)	<.001	43.5 (29.4–57.5)	0.17 (0.08–0.25)	<.001	44.9 (24–65.8)
R5–R20	0.13 (0.1–0.166)	<.001	272.2 (8.1–531.8)	0.12 (0.06–0.19)	<.001	248.2 (11.5–484.8)
Respiratory reactance						
Area under the curve	1.80 (1.12–2.48)	<.001	436.4 (246–625)	1.97 (0.97–2.97)	<.001	484.8 (182.2–787.5)
Resonant frequency (Hz)	8.41 (5.92–10.9)	<.001	67.8 (40.9–94.7)	8.57 (5.04–12.1)	<.001	56.3 (21.3–91.3)

Abbreviations: CI, confidence interval; FEF_{25%–75%}, forced expiratory flow from 25% to 75%; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; R5, total airway resistance at 5 Hz; R5–R20, peripheral airway resistance at 5 minus 20 Hz.

spirometry and IOS indices. Subgroup analysis by categorization by the ACQ score also was performed. Linear regression analysis of the percentage of change of FEV₁ and R5 also was performed.

Results

Within the original study,¹⁰ 21 participants were randomized, 18 of whom (10 women and 8 men) completed the protocol. All 18 patients were used in this analysis. Mean age was 36 years (SEM 4 years). Baseline characteristics are listed in Table 1.

For methacholine and histamine challenges, at the PC₂₀ threshold, the mean percentages of change in R5 were similar (as a measurement of total airway resistance) at 43.5% (95% confidence interval [CI] 29.4–57.5, $P < .001$) and 44.9% (95% CI 24.0–65.8, $P < .001$), respectively. The magnitude of percentage of change demonstrated in R5 was greater than observed for FEV₁ in the 2 bronchial challenge tests, which were recorded as 23.3% (95% CI 18.7–27.9, $P < .001$) after the methacholine challenge and 25.9% (95% CI 21.0–30.8, $P < .001$) after the histamine challenge. Figure 1 shows values for FEV₁ and R5 before and after the methacholine challenge when displayed as percentages of predicted values.

Furthermore, the magnitude of change seen was greater for all IOS indices (R5, R5–20, area under curve, and resonant frequency) compared with spirometry (FEV₁, forced expiratory flow from 25% to 75%, and forced vital capacity; Table 2). Linear regression of percentage of change of FEV₁ vs R5 for histamine challenge testing showed a degree of correlation ($r = 0.262$, $P = .03$; Fig 2).

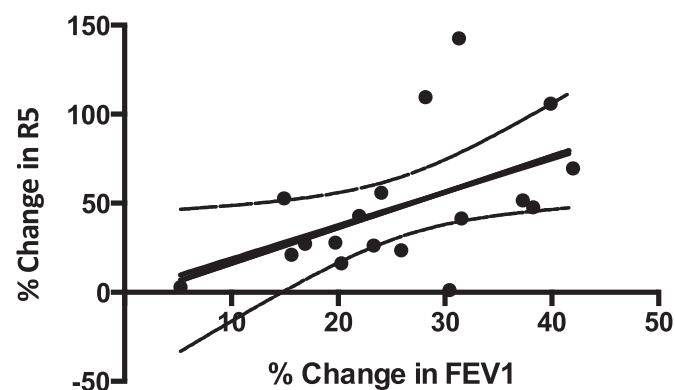


Figure 2. Linear regression of percentage of change of forced expiratory volume in 1 second (FEV₁) vs total airway resistance at 5 Hz (R5).

Stratification by ACQ score into those who had well-controlled (ACQ score <0.75) vs poorly controlled (ACQ score >0.75) asthma showed no difference in the magnitude of bronchoconstrictor response. The mean percentages of change for FEV₁ before and after methacholine testing were recorded as 22.9% (95% CI 19–26.9) for an ACQ score lower than 0.75 and 23.6% (95% CI 15.1–32.2) for a score higher than 0.75. Furthermore, the mean percentages of change for R5 before and after methacholine testing were recorded as 47.4% (95% CI 26.1–68.8) for an ACQ score lower than 0.75 and 40.3% (95% CI 17.9–62.7) for a score higher than 0.75. Figure 3 shows the values for FEV₁ and R5 before and after the methacholine challenge when displayed as percentages of predicted values as stratified by the ACQ score.

Discussion

To the authors' knowledge, this is the first study in adult patients with asthma to directly compare the effects on IOS measurements recorded concurrently with spirometry during methacholine and histamine bronchial challenge testing. Significant effects were observed for all IOS measurements during bronchial challenge testing, with no significant differences observed through the use of methacholine or histamine. The assessment of AHR by PC₂₀ through the FEV₁ measurement is a well-established marker of disease severity that is used extensively in clinical practice and trials. Within the present study, the lower CI for the increase in total airway resistance measured by R5 (after the methacholine bronchial challenge) was approximately 29%, corresponding to a lower CI for FEV₁ of approximately 19%. Therefore, the authors postulate whether the development of a "PC₃₀" threshold for R5 could be developed and used in patients who cannot perform the effort-dependent maneuvers.

Previous studies have shown a relation between spirometry and IOS in mild to moderate asthma.^{12,13} In line with previous studies,¹² the authors found significant effects on small airway measurements (R5–R20) during standardized bronchial challenge testing. Small airway dysfunction within asthma is becoming recognized as a distinct clinical phenotype associated with poor asthma control.¹⁴ In the present study, no significant difference was observed in spirometry or IOS indices after bronchial challenge testing when stratified by asthma control, presumably reflecting the relatively narrow range of ACQ values overall as evidenced by a mean ACQ score of 0.8 (95% CI 0.6–1.1).

In conclusion, the authors have demonstrated the potential role of IOS measurements during bronchial challenge testing to methacholine and histamine in adult patients with asthma. Further

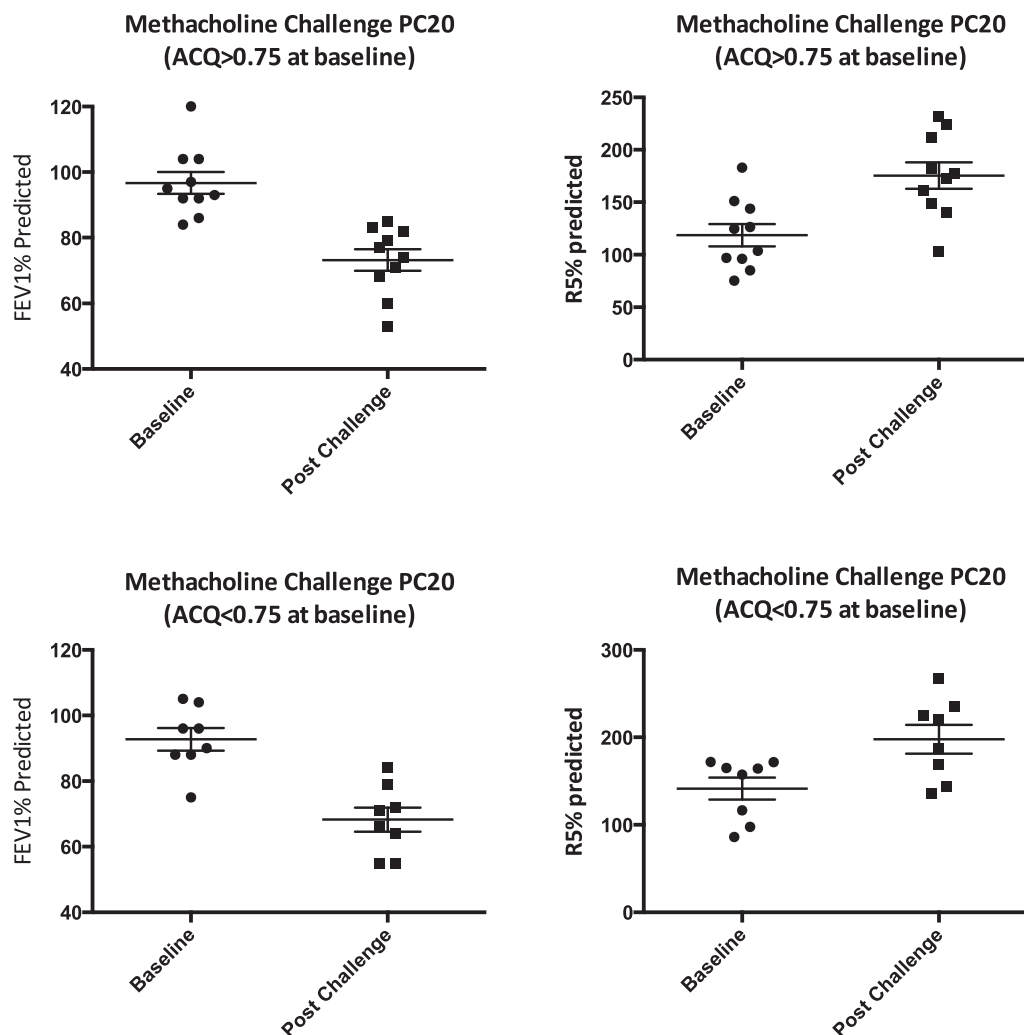


Figure 3. Bronchoconstrictor response stratified by an Asthma Control Questionnaire (ACQ) score lower vs higher than 0.75. FEV₁, forced expiratory volume in 1 second; PC₂₀, provocation concentration that causes a decrease in forced expiratory volume in 1 second of 20%; R5, total airway resistance at 5 Hz.

population-based challenge studies are required to more precisely define appropriate thresholds for IOS measurements.

References

- [1] Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing—1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med.* 2000;161:309–329.
- [2] Oostveen E, MacLeod D, Lorino H, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Respir J.* 2003;22:1026–1041.
- [3] Houghton CM, Woodcock AA, Singh D. A comparison of lung function methods for assessing dose–response effects of salbutamol. *Br J Clin Pharmacol.* 2004;58:134–141.
- [4] Houghton CM, Woodcock AA, Singh D. A comparison of plethysmography, spirometry and oscillometry for assessing the pulmonary effects of inhaled ipratropium bromide in healthy subjects and patients with asthma. *Br J Clin Pharmacol.* 2005;59:152–159.
- [5] Nair A, Ward J, Lipworth BJ. Comparison of bronchodilator response in patients with asthma and healthy subjects using spirometry and oscillometry. *Ann Allergy Asthma Immunol.* 2011;107:317–322.
- [6] Short PM, Williamson PA, Lipworth BJ. Sensitivity of impulse oscillometry and spirometry in beta-blocker induced bronchoconstriction and beta-agonist bronchodilation in asthma. *Ann Allergy Asthma Immunol.* 2012;109:412–415.
- [7] Song TW, Kim KW, Kim ES, et al. Utility of impulse oscillometry in young children with asthma. *Pediatr Allergy Immunol.* 2008;19:763–768.
- [8] Yoon JW, Shin YH, Jee HM, et al. Useful marker of oscillatory lung function in methacholine challenge test—comparison of reactance and resistance with dose–response slope. *Pediatr Pulmonol.* 2014;49:521–528.
- [9] Schulze J, Smith HJ, Fuchs J, et al. Methacholine challenge in young children as evaluated by spirometry and impulse oscillometry. *Respir Med.* 2012;106:627–634.
- [10] Short PM, Williamson PA, Anderson WJ, Lipworth BJ. Randomized placebo-controlled trial to evaluate chronic dosing effects of propranolol in asthma. *Am J Respir Crit Care Med.* 2013;187:1308–1314.
- [11] Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J.* 2005;26:319–338.
- [12] Alfieri V, Aiello M, Pisi R, et al. Small airway dysfunction is associated to excessive bronchoconstriction in asthmatic patients. *Respir Res.* 2014;15:86.
- [13] Boudewijn IM, Telenga ED, van der Wiel E, et al. Less small airway dysfunction in asymptomatic bronchial hyperresponsiveness than in asthma. *Allergy.* 2013;68:1419–1426.
- [14] Lipworth B, Manoharan A, Anderson W. Unlocking the quiet zone: the small airway asthma phenotype. *Lancet Respir Med.* 2014;2:497–506.