



Sensitivity of impulse oscillometry and spirometry in beta-blocker induced bronchoconstriction and beta-agonist bronchodilatation in asthma

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ABSTRACT

Background: Impulse oscillometry (IOS) provides an alternative method of assessing pulmonary function to conventional spirometry.

Objective: To compare the sensitivities of IOS and spirometry in assessing bronchoconstriction to propranolol and bronchodilation with salbutamol.

Methods: A post-hoc analysis of a randomized placebo-controlled crossover study was performed. Patients with mild-to-moderate persistent stable asthma taking 1,000 µg/day or less beclomethasone dipropionate equivalent received 10 or 20 mg of oral propranolol followed by histamine challenge, with recovery to nebulized salbutamol (5 mg). Spirometry and IOS were measured before and 2 hours after beta-blocker, post histamine, and 20 minutes post-salbutamol. Pre versus post percent change (95%CI) values were compared, and standardized response means (SRM) were calculated to assess the “signal to noise” of each test.

Results: Thirteen participants (mean age, 34 years) completed the protocol. Eleven participants received 20 mg of propranolol; 2 received 10 mg, because this dose caused more than 10% decrease in forced expiratory volume in 1 second (FEV₁) on the test-dose algorithm. All IOS indices (R5, R5-R20, AX, RF) showed significant worsening of airways resistance or reactance to propranolol. FEV₁ but not FEF₂₅₋₇₅ showed significant deterioration after beta-blocker (mean percent change, 4.6% and 6.2%). The magnitude of change was consistently higher for parameters of IOS, with the largest change being observed with R5 and RF (mean percent change, 30.8% and 39.4%). The SRMs for IOS outcomes were better than for spirometry. All measures of lung function showed significant bronchodilator response, with the best SRMs seen in R5 and RF.

Conclusion: IOS is a more sensitive response outcome than spirometry with respect to bronchoconstriction to oral propranolol and bronchodilatation after salbutamol in patients with mild to moderate asthma.

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Introduction

Spirometry and impulse oscillometry (IOS) are 2 distinct methods of assessing lung function and provide means of measuring change to airway tone after either a bronchoconstricting or a bronchodilating stimulus. Unlike conventional spirometry, which is an effort-dependent test, IOS is performed at tidal volume during normal breathing, which assesses several components of respiratory physiology, namely, airway resistance and pulmonary reactance.¹

In the United Kingdom, the use of beta-blockers in patients with asthma, regardless of drug selectivity is contraindicated because of the potential risk of bronchospasm.^{2,3} Although the effects on spirometry and predominantly forced expiratory volume in 1

second (FEV₁) have been extensively studied after beta-blocker use,⁴ the effects of beta-blocker–induced bronchoconstriction on IOS are less well known.

IOS is known to be a sensitive marker of airway dysfunction, but it is commonly associated with a wider variation than spirometry.⁵ We have previously demonstrated that IOS is more sensitive than spirometry at demonstrating beta-blocker–induced bronchoconstriction⁶; however, we have not accounted for the variability associated with IOS. When considering the relative sensitivities of spirometry and IOS, one must determine the “signal to noise” ratio of each test, thereby allowing an analysis of both the effect size and responsiveness of each test.

Accounting for the variability of each test, through calculation of standardized response means, we compared the relative sensitivities of IOS and spirometry in the assessment of bronchoconstriction to propranolol and bronchodilation to salbutamol.

Methods

A post hoc analysis of lung function data from the placebo limb of a randomized placebo-controlled double-blind crossover trial

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was performed. The methods within the reference study have been described previously; however, we have reiterated the key details and measurements specific to this study.⁶ Patients with mild-to-moderate persistent stable asthma taking 1,000 µg/day or less beclomethasone dipropionate equivalent of inhaled corticosteroids, FEV₁ greater than 80% predicted, aged 18 to 65 years, who had airway hyper-responsiveness to histamine challenge were recruited. All participants were nonsmokers.

Subjects were invited to participate from a list of known volunteers who had expressed an interest to take part in clinical trials within our department. Potential participants received a written participant information sheet detailing the trial requirements and the extent of their participation before attending for a screening visit. Informed written consent was obtained after discussion with a respiratory physician.

On the study visit, each participant received a single dose of 10 or 20 mg of oral propranolol followed by histamine bronchial challenge testing 4 hours later, with recovery to nebulized salbutamol 5 mg. Spirometry and IOS were measured before and 2 hours after beta-blocker, after histamine, and 20 minutes after salbutamol.

Spirometry and impulse oscillometry were performed in accordance with published guidelines.^{1,7} IOS is an effort-independent method of assessing lung function by the use of sound waves superimposed on normal breathing cycles. A super Spiro spirometer (Micro Medical, Basingstoke, United Kingdom) and IOS Jaeger Masterscreen (Wurzburg, Germany) were used. Histamine bronchial challenge testing was performed with the provocative dose of histamine required to cause a 10% decrease in FEV₁ being calculated. A Mefar dosimeter was used with histamine concentrations of 0.3125 to 40 mg/mL.

Data were analyzed for normality with Shapiro-Wilk tests and Boxplots. Pre vs post percentage change (95% CI) values were calculated and compared with paired Student *t*-tests for spirometry and IOS indices after bronchoconstriction to propranolol and bronchodilatation to salbutamol. Standardized response means (SRM) were also calculated. SRM is a relative measure of effect size and responsiveness. It allows the expression of the signal of change in an outcome relative to its variability.⁸ SRMs therefore express the signal (ie, mean) to noise (ie, standard deviation) ratio

Table 1

Demographics

Subject/Sex	Age	FEV ₁ %	R5%	Histamine PC ₁₀ (mg/mL)	BDP Equivalent Daily Dose (µg)
1/F	20	100	174	0.44	400
2/F	40	106	136	8.41	800
3/F	42	106	81	7.07	800
4/F	19	96	127	0.14	400
5/F	44	104	160	1.98	800
6/F	23	118	97	8.91	1,000
7/M	24	86	160	2.18	400
8/M	44	92	112	1.89	1,000
9/M	30	92	89	1.77	400
10/M	63	92	114	0.71	200
11/M	30	97	153	10.59	800
12/M	26	90	183	0.35	400
13/M	34	92	169	0.28	800
Mean (SEM)	34 (3)	98 (2)	135 (9)	3.44 (1.1)	631 (75)

Abbreviations: FEV₁, forced expiratory volume in 1 second; R5, resistance at 5Hz; PC₁₀, provocative concentration required to achieve 10% fall in FEV₁; BDP, beclomethasone dipropionate equivalent. Data shown as % predicted for age, sex, race.

and are calculated as mean change in an outcome divided by the standard deviation of the difference. Ideally, an SRM would be greater than unity; however, an SRM of approximately 0.20 is considered small, one of 0.50 indicates moderate responsiveness, and those of 0.80 or more are considered highly sensitive. Because SRMs are standardized scores, the SRM for spirometry can be compared directly with the SRMs for impulse oscillometry.⁸ All statistical analyses were performed using SPSS version 17.

Results

Of 26 participants screened, after application of study inclusion criteria, 15 were enrolled. A total of 13 participants (mean age, 34 years) completed the study (Table 1). Two participants withdrew because they could not complete the study visits for personal reasons. Eleven participants received 20 mg of oral propranolol, 2 received 10 mg because this dose was sufficient to cause more than a 10% fall in FEV₁ on the test-dose algorithm. There were no adverse events after beta-blocker ingestion.

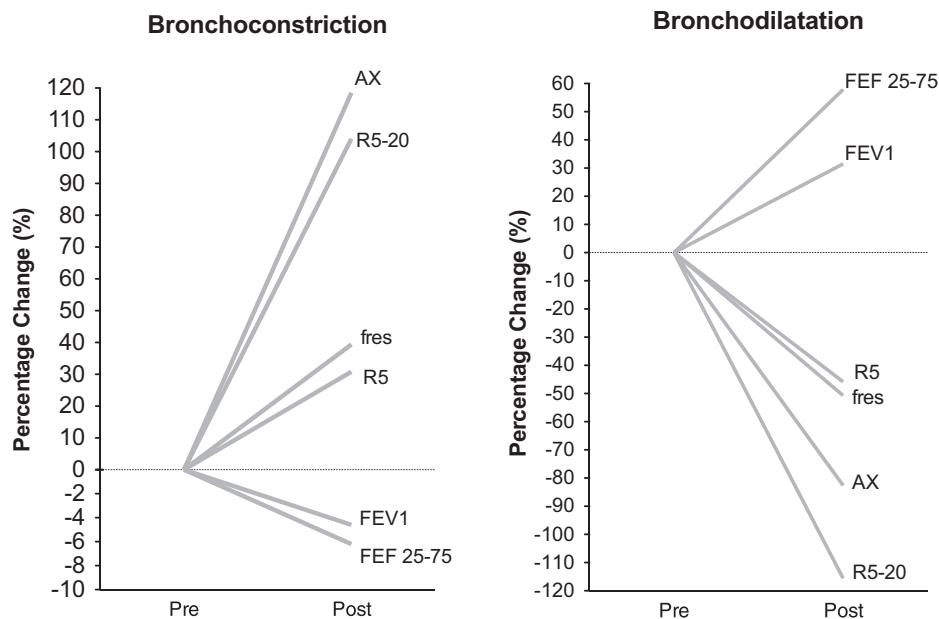


Figure 1. Percentage change for spirometry (FEV₁, FEF₂₅₋₇₅) and impulse oscillometry (AX, R5-20, R5, fres) for the bronchoconstrictor response to propranolol and the bronchodilator response to salbutamol.

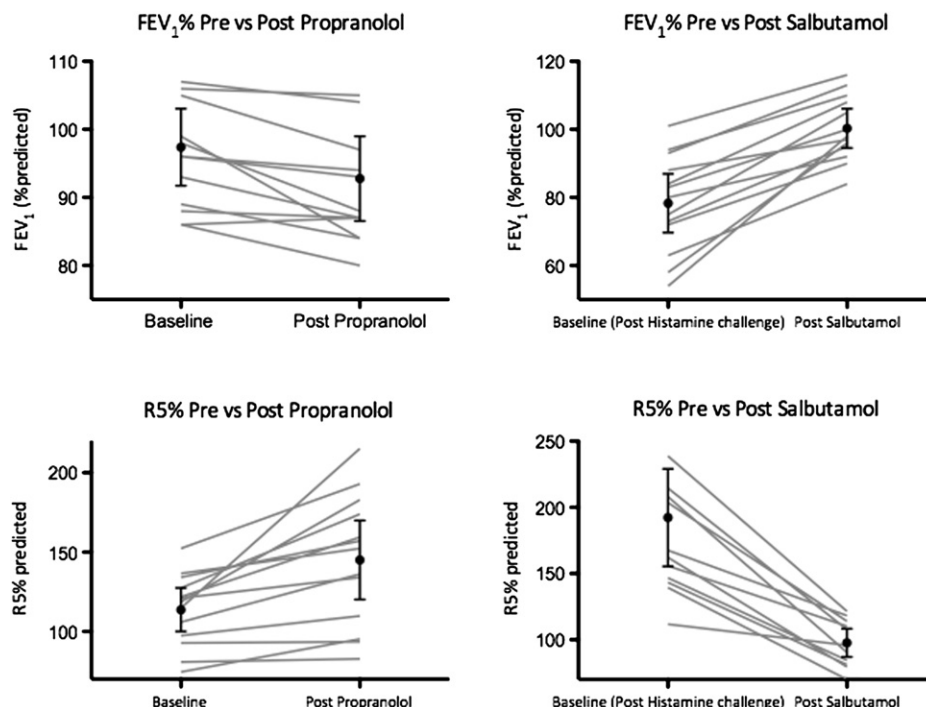


Figure 2. Individual participant percentage change for FEV₁% and R5% bronchoconstrictor response to propranolol and the bronchodilator response to salbutamol. Data displayed with respective means and 95%CI.

All IOS indices showed a greater magnitude of response to propranolol (ie, as percent change) compared with spirometry. The greatest magnitudes of change were observed in the difference between airway resistance at 5Hz (R5) and 20Hz (R20) and area (AX), measurements of small airway resistance and pulmonary reactance. With regards to bronchodilator response, forced expiratory flow 25%–75% (FEF_{25–75}) demonstrated a greater magnitude of change to salbutamol compared with R5 and fres; however, the greatest magnitude of change was again seen in R5–20 and AX (Fig 1).

All IOS indices (R5, R5–R20, AX, resonant frequency [fres]) showed significant worsening of airways resistance or reactance to propranolol. FEV₁ and not FEF_{25–75} showed significant deterioration after beta-blocker. Individual participant response after propranolol and salbutamol and their effects on FEV₁ and R5% predicted are shown in Figure 2.

The SRMs for IOS outcomes were higher than those for spirometry, indicating a superior signal-to-noise ratio, with the

highest SRM seen with R5. All measures of IOS and spirometry showed a significant bronchodilator response after salbutamol, with the greatest SRMs seen in fres and R5 (Table 2).

Discussion

To our knowledge, this is the first study, accounting for test variability, to directly compare the sensitivities of impulse oscillometry and conventional spirometry when using beta-blockers as the bronchoconstricting stimulus. Beta-blockers are avoided in asthma because of concerns regarding potential bronchospasm.⁹ Subsequently, trials involving beta-blocker use in patients with asthma need to be performed with safety as the primary focus. Participants enrolled into studies using contraindicated medications in asthma subsequently have mild-to-moderate disease and thereby relatively preserved spirometry.¹⁰ As a result of this, spirometry may be regarded as

Table 2
Spirometry and impulse oscillometry

Outcome	Bronchoconstriction			Bronchodilatation		
	Mean difference (95% CI), P value	Mean percentage change (95% CI)	Standardized response mean	Mean difference (95% CI), P value	Mean percentage change (95% CI)	Standardized response mean
Spirometry						
FEV ₁ (L)	0.16 (0.05–0.27), P = .009	4.6% (1.9–7.3)	0.86	0.77 (0.49–1.05), P < .001	31.5% (18.2–44.7)	1.67
FEF _{25–75} (L)	0.21 (–0.06–0.46), P = .116	6.2% (–0.2–12.6)	0.47	1.08 (0.63–1.55), P < .001	57.9% (29.1–86.7)	1.42
Impulse oscillometry						
R5 (Airway resistance at 5 Hz) (kPa L/s)	0.099 (0.054–0.144), P < .001	30.8% (14.01–47.6)	1.32	0.280 (0.189–0.37), P < .001	45.8% (36.7–55)	1.87
(Total airway resistance)						
R5–R20 (difference)	0.052 (0.020–0.084), P = .004	104.1% (22.6–185.6)	1.05	0.171 (0.095–0.246), P < .001	115.6% (55.6–175.7)	1.43
(Small airways resistance)						
AX (area)	0.496 (0.162–0.831), P = .007	118.5% (37.2–200)	0.94	1.88 (0.933–2.827), P = .001	82.6% (73.9–91.3)	1.26
(Respiratory reactance)						
RF (Resonant frequency) (Hz)	4.81 (2.24–7.37), P = .002	39.4% (16.6–54.3)	1.13	12.71 (9.1–16.31), P < .001	50.7% (40.7–60.8)	2.13
(Respiratory reactance)						

an insensitive measurement to assess bronchoconstriction and conversely bronchodilatation in these patients.

Although we have previously demonstrated that IOS is a more sensitive measurement for assessing beta blocker–induced bronchoconstriction, we have not accounted for the variability associated with IOS.⁶ Standardized response means are highly informative standardized scores, routinely used to compare differing health-related outcomes, which in the case of this study allows the comparison of spirometry and IOS.^{8,11–13} Reflecting the greater magnitude of change seen with IOS outcomes within our study, the highest standardized response means were also seen with IOS measurements.

Impulse oscillometry is an alternative technique to assess changes in airway tone, which has been shown to be sensitive to measuring bronchodilation to salbutamol and ipratropium within both asthma and chronic obstructive pulmonary disease populations.^{5,14,15} IOS is an effort-independent test, using oscillation of differing sound waves to derive a variety of output measurements, thus determining both the degree of total (R5) and peripheral airway resistance (R5–R20) and pulmonary reactance (AX, fres). IOS does not include the forced expiratory maneuvers required when performing spirometry; as a result, IOS is routinely used to good effect in pediatric populations as an alternative or adjunct to spirometry.¹⁶ Within our study, the greatest magnitude changes to beta-blocker and beta-agonist use were seen within IOS measurements that were reflective of small airway dysfunction, namely R5–R20 and AX. IOS in determining small airway dysfunction has also been used to good effect in assessing asthma control in children.¹⁷ We believe our findings reaffirm the importance of evaluating small airway disease in the individual with asthma and demonstrate the ability of IOS to examine both small and large airway dysfunction independently in those with relatively preserved spirometry.

In conclusion, IOS has been shown to be a more sensitive marker of bronchoconstriction to oral propranolol than spirometry, even when adjusted for greater test variation. This is true for both small changes (propranolol-induced bronchoconstriction) and large changes (salbutamol-induced reversal of histamine). Furthermore, our study provides further evidence that IOS demonstrates a greater bronchodilator response in mild-to-moderate asthmatics in comparison with spirometry.

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