

Clinical Communications

Impulse oscillometry bronchodilator response and asthma control

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Clinical implications

- Impulse oscillometry is more sensitive than spirometry in detecting bronchodilator response in poorly controlled asthma.

Bronchodilator response (BDR) is conventionally defined as a greater than 12% and greater than 200 mL increase from baseline in FEV₁ measured using spirometry.¹ Forced expiratory flow between 25% and 75% of forced vital capacity (FEF₂₅₋₇₅) is thought to reflect volume-dependent closure of the small airways. Impulse oscillometry (IOS) is an effort-independent forced oscillation technique (FOT) using sound waves superimposed on normal tidal breathing, requiring minimal patient cooperation and is therefore more physiological. Persistent BDR is associated with worse asthma control, albeit lung function is often disconnected from patient-reported symptoms.^{2,3} Because of the ease of performing IOS measurements, IOS BDR threshold had been widely assessed in pediatric pulmonology.⁴ However, IOS BDR thresholds in adults are still not clearly defined. We therefore sought to determine the difference between spirometry and IOS BDR in patients with well- and poorly controlled asthma.

Retrospectively, we evaluated 57 patients with an established diagnosis of persistent asthma who attended the Scottish Centre for Respiratory Research (Dundee, United Kingdom) for screening into clinical trials. The six-item Asthma control questionnaire (ACQ-6), fractional exhaled nitric oxide (FeNO), and lung function tests including spirometry (Micromedical, Chatham, United Kingdom) and IOS (Jaeger MasterScreen, Carefusion Technologies, Hoechst, Germany) were performed before and after the administration of albuterol 400 µg in triplicate according to European Respiratory Society guidelines, with IOS always performed first.⁵ Consents were obtained from all patients for access to their screening data.

We used an ACQ-6 score cutoff point of 1.0 to define poor asthma control.⁶ A comparison was made according to pre-defined cutoff points for IOS BDR values: area under the reactance curve (AX) less than 35% versus greater than or equal to 35%; reactance at 5 Hz (X5) less than 15% versus greater than or equal to 15%; resonance frequency (F_{res}) less than 15% versus greater than or equal to 15%; and resistance at 5 Hz (R5) less than 15% versus greater than or equal to 15%. The comparisons were conducted using independent Student's *t* test, with alpha error set at 0.05 (2 tailed). Receiver-operator characteristic (ROC) curves were plotted to assess sensitivity and specificity of IOS and spirometry % BDR for detecting poor asthma control.

The mean age was 51 years; FEV₁, 79% predicted; AX, 1.35 kPa/L/s; R5, 0.41 kPa/L/s; resistance at 20 Hz, 0.37 kPa/L/s;

difference in resistance at 5 and 20 Hz, 0.12 kPa/L/s; ACQ-6 score, 1.38; and FeNO 38 ppb. Mean inhaled corticosteroid (beclomethasone equivalent) dose was 670 µg; and 68% were taking long-acting beta-agonist; 11%, long-acting muscarinic antagonist; 25%, leukotriene receptor antagonist; and 4%, theophylline.

Using an ACQ-6 score less than 1 and greater than or equal to 1 to compare well- and poorly controlled asthma, we found that there were significant differences in % BDR with FEV₁, AX, X5, F_{res} , and R5 (Table I). In the subgroup with a preserved FEV₁ of greater than or equal to 80% (*n* = 30), % BDR values for AX, X5, R5, and FEF₂₅₋₇₅ were significantly higher in poorly controlled asthma. In the cohort with no spirometry evidence of BDR as represented by a FEV₁ BDR of less than 12% and less than 200 mL (*n* = 37), AX, X5, and R5 were significantly higher in those with poorly controlled asthma. FeNO was also significantly higher in the poorly controlled group.

Asthma control (as mean ACQ-6 score) was found to be significantly worse on comparing % BDR for AX less than 35% versus greater than or equal to 35%: 0.92 versus 1.79 (95% CI for difference, 0.34-1.40; *P* < .01); X5 less than 15% versus greater than or equal to 15%: 0.77 versus 1.73 (95% CI, 0.48-1.44; *P* < .001); F_{res} less than 15% versus greater than or equal to 15%: 0.93 versus 1.76 (95% CI, 0.31-1.35; *P* < .01); R5 less than 15% versus greater than or equal to 15%: 0.90 versus 1.79 (95% CI, 0.37-1.40; *P* < .01); and FEV₁ less than 12% versus greater than or equal to 12%: 1.22 versus 2.22 (95% CI, 0.26-1.75; *P* < .01).

In patients with preserved FEV₁, ACQ-6 scores were also significantly higher when comparing % BDR for AX at a cutoff point of 35%: 0.73 versus 1.60 (95% CI, 0.25-1.49; *P* < .01); X5 15%: 0.71 versus 1.56 (95% CI, 0.26-1.44; *P* < .01); F_{res} 15%: 0.84 versus 1.52 (95% CI, 0.07-1.29; *P* < .05); and R5 15%: 0.81 versus 1.56 (95% CI, 0.16-1.35; *P* < .05). These differences in ACQ-6 score all exceeded the minimal clinically important difference of 0.5.

ROC curve analysis for predicting poor asthma control with IOS % BDR, namely, AX, X5, F_{res} , and R5, demonstrated fair accuracy, with area under the ROC curve between 0.70 and 0.80 (Table II). Poor asthma control was detected with a BDR of 35% for AX, 14% for X5, 15% for F_{res} , and 15% for R5. The corresponding sensitivity and specificity values are presented in Table II. The area under the ROC curve values were 0.69 (95% CI, 0.55-0.83; *P* < .05) and 0.66 (95% CI, 0.51-0.80; *P* < .05) with sensitivity: 23% and 45% as well as specificity: 96% and 77% for FEV₁ 12% and 200 mL BDR, respectively.

Our results demonstrate that IOS % BDR for airway reactance (AX, X5), F_{res} , and resistance at 5 Hz were all associated with poor asthma control. This was also observed with FEV₁ but not FEF₂₅₋₇₅ in all patients, whereas in those patients with preserved FEV₁, poor control was associated with increased % BDR for FEF₂₅₋₇₅. This is consistent with a previous study comparing relative bronchoconstrictor and bronchodilator response using IOS and spirometry in patients with asthma.⁷ Another study also reported similar findings in asthma, with the relative mean percentage change in response to albuterol 400 µg being 6% and 34% for FEV₁ and R5, respectively.⁸

TABLE I. Comparisons between well- and poorly controlled asthma in IOS and spirometry %BDR as well as FeNO

% BDR and FeNO	Overall		FEV ₁ ≥ 80%		FEV ₁ BDR < 12% and <200 mL	
	ACQ score < 1	ACQ score ≥ 1	ACQ score < 1	ACQ score ≥ 1	ACQ score < 1	ACQ score ≥ 1
FEV ₁ % BDR	5	8	5	6	4	4
	(1 to 6)*		(−4 to 1)		(−3 to 1)	
FEF ₂₅₋₇₅ % BDR	12	17	9	22	11	16
	(−12 to 2)		(−21 to −4)†		(−13 to 3)	
AX % BDR	26	49	22	45	22	43
	(11 to 34)‡		(5 to 40)*		(6 to 35)†	
X5 % BDR	12	28	7	28	9	25
	(8 to 25)‡		(9 to 33)†		(4 to 26)†	
F _{res} % BDR	14	22	13	19	13	19
	(1 to 14)*		(−4 to 15)		(−14 to 1)	
R5 % BDR	10	19	8	18	9	18
	(4 to 14)†		(4 to 17)†		(3 to 15)†	
R20 % BDR	10	12	7	13	8	12
	(−2 to 7)		(−11 to 0.26)		(−10 to 2)	
R5-R20 % BDR	−27	39	23	34	26	31
	(−6 to 30)		(−15 to 38)		(−28 to 18)	
FeNO (ppb)	25	49	22	52	24	46
	(10 to 37)†		(8 to 52)*		(3 to 41)*	

R5-R20, Difference in resistance at 5 and 20 Hz; R20, resistance at 20 Hz.

Values are presented as mean (95% CI for difference).

P* < .05.†*P* < .01.‡*P* < .001.TABLE II.** ROC curve analysis for predicting poor asthma control with IOS % BDR

IOS measurements	% BDR	% sensitivity	% specificity	AUC (95% CI)
R5	15	77	73	0.77 (0.63-0.91)*
AX	35	77	73	0.78 (0.65-0.91)†
X5	14	84	61	0.76 (0.63-0.89)*
F _{res}	15	71	65	0.71 (0.57-0.86)*

AUC, Area under the ROC curve.

**P* < .01.†*P* < .001.

Notably, the IOS % BDR in the subgroup of patients with asthma with preserved FEV₁ was significantly higher in the poorly controlled group. This perhaps reflects that alterations in small airway geometry are more closely related to asthma control. The persistently higher FeNO in the poorly controlled group mirrors underlying type 2 inflammation and is associated with a greater degree of IOS BDR.

A recent study also concluded that the reactance components of FOT were more sensitive than spirometry in detecting poor asthma control.⁹ However, they used reference values for FOT BDR derived from healthy subjects, which would not be applicable to patients with asthma in whom a greater reversibility would be expected because of alterations in resting bronchomotor tone and airway geometry.

We recognize the main limitation of our study as being retrospective and cross-sectional with a relatively small sample size. However, our findings are consistent with previous studies with larger sample sizes and controlled trials.^{7,8} Our study may have clinical implications suggesting that effort-independent IOS may provide complementary information on BDR in patients with poorly controlled asthma, especially in those with preserved FEV₁.

In conclusion, bronchodilator response using IOS measurements is associated with poor asthma control. IOS is more sensitive than spirometry in detecting bronchodilator response in poorly controlled asthma especially in those patients with a preserved FEV₁.

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Conflicts of interest: C. R.W. Kuo reports personal fees (talks) from AstraZeneca; personal fees (advisory board) from Circassia; and personal fees (talks) from Chiesi (talks, attending British Thoracic Society [BTS] meetings) outside of the submitted work. R. Chan declares that he has no relevant conflicts of interest. B. Lipworth reports nonfinancial support (equipment) from GlaxoSmithKline; grants, personal fees (consulting, talks, and advisory board), and other support (attending American Thoracic Society and European Respiratory Society [ERS] meetings) from AstraZeneca; grants, personal fees (consulting, talks, and advisory board), and other support (attending ERS meetings) from Teva; personal fees (consulting) from Lupin, Glenmark, Vectura, Dr Reddy, and Sandoz, in relation to the submitted work; grants, personal fees (consulting, talks, and advisory board), and other support (attending BTS meetings) from Boehringer Ingelheim; grants and personal fees (advisory board and talks) from Mylan; grants and personal fees (consulting) from Sanofi, outside of the submitted work; and that his son is presently an employee of AstraZeneca.

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REFERENCES

- Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948-68.
- Heffler E, Crimi C, Campisi R, Sichili S, Nicolosi G, Porto M, et al. Bronchodilator response as a marker of poor asthma control. *Respir Med* 2016;112:45-50.

3. Barnes PJ, Szeffler SJ, Reddel HK, Chipps BE. Symptoms and perception of airway obstruction in asthmatic patients: clinical implications for use of reliever medications. *J Allergy Clin Immunol* 2019;144:1180-6.
4. Calogero C, Simpson SJ, Lombardi E, Parri N, Cuomo B, Palumbo M, et al. Respiratory impedance and bronchodilator responsiveness in healthy children aged 2-13 years. *Pediatr Pulmonol* 2013;48:707-15.
5. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
6. Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med* 2006;100:616-21.
7. Short PM, Williamson PA, Lipworth BJ. Sensitivity of impulse oscillometry and spirometry in beta-blocker induced bronchoconstriction and beta-agonist bronchodilatation in asthma. *Ann Allergy Asthma Immunol* 2012; 109:412-5.
8. 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;107:317-22.
9. Cottee AM, Seccombe LM, Thamrin C, King GG, Peters MJ, Farah CS. Bronchodilator response assessed by the forced oscillation technique identifies poor asthma control with greater sensitivity than spirometry. *Chest* 2020;157:1435-41.