

University of Dundee

Impulse oscillometry bronchodilator response and asthma control

Kuo, Chris RuiWen; Chan, Rory; Lipworth, Brian

Published in:
The Journal of Allergy and Clinical Immunology: In Practice

DOI:
[10.1016/j.jaip.2020.07.031](https://doi.org/10.1016/j.jaip.2020.07.031)

Publication date:
2020

Licence:
CC BY-NC-ND

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):
Kuo, C. R., Chan, R., & Lipworth, B. (2020). Impulse oscillometry bronchodilator response and asthma control. *The Journal of Allergy and Clinical Immunology: In Practice*, 8(10), 3610-3612.
<https://doi.org/10.1016/j.jaip.2020.07.031>

General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

1 Title: Impulse oscillometry bronchodilator response and asthma control
2 Authors: Dr Chris RuiWen Kuo MBChB
3 Dr Rory Chan MBChB
4 Dr Brian Lipworth MD
5 Affiliation: Scottish Centre for Respiratory Research
6 University of Dundee
7 Ninewells Hospital and Medical School
8 Dundee, DD1 9SY
9 Scotland, UK
10 Corresponding author: Dr Brian Lipworth
11 Scottish Centre for Respiratory Research
12 University of Dundee
13 Ninewells Hospital and Medical School
14 Dundee, DD1 9SY
15 Scotland, UK
16 b.j.lipworth@dundee.ac.uk
17 Office: +44 1382 383188
18 Conflicts of interest:
19 Dr Lipworth reports non-financial support (equipment) from GSK; grants, personal fees (consulting, talks
20 and advisory board), other support (attending ATS and ERS) and from AstraZeneca, grants, personal fees
21 (consulting, talks, advisory board), other support (attending ERS) from Teva, personal fees (consulting
22 from Lupin, personal fees (consulting) from Glenmark, personal fees (consulting) from Vectura, personal
23 fees (consulting) from Dr Reddy, personal fees (consulting) from Sandoz, in relation to the submitted
24 work; grants, personal fees (consulting, talks, advisory board), other support (attending BTS) from
25 Boehringer Ingelheim, grants and personal fees (advisory board and talks) from Mylan, grants, personal
26 fees (consulting) from Sanofi, outside of the submitted work; and son of BJL is presently an employee of
27 AstraZeneca.
28 Dr Chan has no relevant conflicts of interest.
29 Dr Kuo reports personal fees (talks) from AstraZeneca, personal fees (advisory board) from Circassia,
30 personal fees (talks) in relation to the submitted work, and other support from Chiesi (talks, attending
31 BTS) outside of the submitted work.
32 Clinical implications: IOS is more sensitive than spirometry in detecting bronchodilator response in
33 poorly controlled asthma.

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

44 Retrospectively, we evaluated 57 patients with an established diagnosis of persistent asthma who
45 attended the Scottish Centre for Respiratory Research (Dundee, UK) for screening into clinical trials.
46 Asthma control questionnaire (ACQ-6), fractional exhaled nitric oxide (FeNO) and lung function tests
47 including spirometry (Micromedical, Chatham, United Kingdom) and IOS (Jaeger MasterScreen,
48 Carefusion Technologies) were performed pre and post albuterol 400µg in triplicate according to ERS
49 guidelines, with IOS always performed first.⁵ Consents were obtained from all patients for access to their
50 screening data.

51 We used an ACQ-6 cut point of 1.0 to define poor asthma control.⁶ A comparison was made according to
52 pre-defined cut points for IOS BDR values: area under the reactance curve (AX) <35% vs ≥35%; reactance
53 at 5Hz (X5) <15% vs ≥15%; resonance frequency (Fres) <15% vs ≥15% and resistance at 5Hz (R5) <15% vs
54 ≥15%. The comparisons were conducted using Independent Student's T test with alpha error set at 0.05
55 (2 tailed). Receiver operator characteristic (ROC) curves were plotted to assess sensitivity and specificity
56 of IOS and spirometry % BDR for detecting poor asthma control.

57 The mean age was 51 years; FEV₁ 79% predicted; AX 1.35 kPa/L; R5 0.41 kPa/L/s; R20 0.37 kPa/L/s; R5-
58 R20 0.12 kPa/L/s; ACQ-6 1.38 and FeNO 38 ppb. Mean inhaled corticosteroid (beclomethasone
59 equivalent) dose was 670µg; and 68% were taking LABA; 11% LAMA; 25% LTRA; and 4% theophylline.

60 Using an ACQ-6 <1 and ≥1 to compare well and poorly controlled asthma, there were significant
61 differences in % BDR with FEV₁, AX, X5, Fres and R5 (Table 1). In the subgroup with a preserved FEV₁ of
62 ≥80% (n=30), % BDR for AX, X5, R5 and FEF₂₅₋₇₅ were significantly higher in poorly controlled asthma. In
63 the cohort with no spirometry evidence of BDR as represented by a FEV₁ BDR <12% and <200ml (n=37),
64 AX, X5 and R5 were significantly higher in those with poorly controlled asthma. FeNO was also significantly
65 higher in the poorly controlled group.

66 Asthma control (as mean ACQ-6) was significantly worse comparing % BDR for AX <35% vs ≥35%: 0.92 vs
67 1.79 (95%CI for difference 0.34, 1.40;p<0.01); X5 <15% vs ≥15%: 0.77 vs 1.73 (CI 0.48, 1.44;p<0.001); Fres
68 <15% vs ≥15%: 0.93 vs 1.76 (CI 0.31, 1.35;p<0.01); R5 <15% vs ≥15%: 0.90 vs 1.79 (CI 0.37, 1.40;p<0.01);
69 and FEV₁ <12% vs ≥12%: 1.22 vs 2.22 (CI 0.26, 1.75;p<0.01).

70 In patients with preserved FEV₁, ACQ-6 were also significantly higher comparing % BDR for: AX at a cut-
71 point of 35%: 0.73 vs 1.60 (CI 0.25, 1.49;p<0.01); X5 15%: 0.71 vs 1.56(CI 0.26, 1.44;p<0.01); Fres 15%:
72 0.84 vs 1.52(CI 0.07, 1.29;p<0.05) and R5 15%: 0.81 vs 1.56(CI 0.16, 1.35;p<0.05). These differences in
73 ACQ-6 all exceeded the minimal clinical important difference of 0.5.

74 ROC curve analysis for predicting poor asthma control with IOS % BDR, namely AX, X5, Fres and R5,
75 demonstrated fair accuracy with AUC between 0.70-0.80 (Table 2). Poor asthma control was detected
76 with a BDR of 35% for AX; 14% for X5; 15% for Fres; and 15% for R5. The corresponding sensitivity and
77 specificity values are shown in Table 2. The AUC were 0.69(CI 0.55, 0.83;p<0.05) and 0.66(CI 0.51,
78 0.80;p<0.05), sensitivity: 23% and 45%, specificity: 96% and 77% for FEV₁ 12% and 200ml BDR respectively.

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

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

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

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

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

102

103 Word count: 996

104

105

106

107

108

109

110

111 **References**

112 1. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies
113 for lung function tests. *Eur Respir J* 2005; 26:948-68.

114 2. Heffler E, Crimi C, Campisi R, Sichili S, Nicolosi G, Porto M, et al. Bronchodilator response as a
115 marker of poor asthma control. *Respir Med* 2016; 112:45-50.

116 3. Barnes PJ, Szefler SJ, Reddel HK, Chipps BE. Symptoms and perception of airway obstruction in
117 asthmatic patients: Clinical implications for use of reliever medications. *J Allergy Clin Immunol*
118 2019; 144:1180-6.

119 4. Calogero C, Simpson SJ, Lombardi E, Parri N, Cuomo B, Palumbo M, et al. Respiratory impedance
120 and bronchodilator responsiveness in healthy children aged 2-13 years. *Pediatr Pulmonol* 2013;
121 48:707-15.

122 5. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of
123 spirometry. *Eur Respir J* 2005; 26:319-38.

124 6. Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying 'well-controlled' and 'not well-
125 controlled' asthma using the Asthma Control Questionnaire. *Respir Med* 2006; 100:616-21.

126 7. Short PM, Williamson PA, Lipworth BJ. Sensitivity of impulse oscillometry and spirometry in
127 beta-blocker induced bronchoconstriction and beta-agonist bronchodilatation in asthma. *Ann*
128 *Allergy Asthma Immunol* 2012; 109:412-5.

129 8. Nair A, Ward J, Lipworth BJ. Comparison of bronchodilator response in patients with asthma and
130 healthy subjects using spirometry and oscillometry. *Ann Allergy Asthma Immunol* 2011;
131 107:317-22.

132 9. Cottee AM, Seccombe LM, Thamrin C, King GG, Peters MJ, Farah CS. Bronchodilator Response
133 Assessed by the Forced Oscillation Technique Identifies Poor Asthma Control With Greater
134 Sensitivity Than Spirometry. *Chest* 2020; 157:1435-41.

135

136

137

138

139

140

141

142

143

144

145

146

147

148

149 Table 1

	Overall		FEV ₁ ≥ 80%		FEV ₁ BDR <12% and <200ml	
	ACQ <1	ACQ ≥1	ACQ <1	ACQ ≥1	ACQ <1	ACQ ≥1
FEV₁ % BDR	5	8 *(1, 6)	5	6 (-4, 1)	4	4 (-3, 1)
FEF₂₅₋₇₅ % BDR	12	17 (-12, 2)	9	22 **(-21, -4)	11	16 (-13, 3)
AX % BDR	26	49 *** (11, 34)	22	45 *(5, 40)	22	43 **(6, 35)
X5 % BDR	12	28 *** (8, 25)	7	28 **(9, 33)	9	25 **(4, 26)
Fres % BDR	14	22 *(1, 14)	13	19 (-4, 15)	13	19 (-14, 1)
R5 % BDR	10	19 **(4, 14)	8	18 **(4, 17)	9	18 **(3, 15)
R20 % BDR	10	12 (-2, 7)	7	13 (0.26, 11)	8	12 (-10, 2)
R5-R20 % BDR	-27	39 (-6, 30)	23	34 (-15, 38)	26	31 (-28, 18)
FeNO ppb	25	49 **(10, 37)	22	52 *(8, 52)	24	46 *(3, 41)

ACQ = Asthma control questionnaire-6, BDR = bronchodilator response, FEV₁ = forced expiratory volume in 1st second, FEF₂₅₋₇₅ = forced expiratory volume at 25-75% of forced vital capacity, AX = area under the reactance curve, X5 = reactance at 5Hz, Fres = resonance frequency, R5 = resistance at 5Hz, R20 = resistance at 20Hz, R5-R20 = difference in resistance at 5 and 20 Hz, FeNO = fractional exhaled nitric oxide. Values are presented as mean (95% CI for difference).

* p<0.05, ** p<0.01, ***p<0.001

150

151

152 Table 2

	% 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)**
Fres	15	71	65	0.71 (0.57, 0.86)**

BDR = bronchodilator response, AX = area under the reactance curve, X5 = reactance at 5Hz, Fres = resonance frequency, R5 = resistance at 5Hz, AUC = area under the curve, CI = confidence interval. * p<0.05, ** p<0.01, ***p<0.001.

153