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Oscillometry bronchodilator response in adult moderate to severe eosinophilic asthma patients

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RESEARCH LETTER

Oscillometry bronchodilator response in adult moderate to severe eosinophilic asthma patients: A prospective cohort study

To the Editor,

The presence of bronchodilator response (BDR) is one of the key hallmarks in diagnosing asthma and is traditionally defined as a >200 ml and >12% improvement in spirometry forced expiratory volume in 1 s (FEV_1) following short acting beta agonist therapy. Patients who demonstrate BDR typically have higher levels of airway inflammation, poorer asthma control and a greater spirometric response to inhaled corticosteroid (ICS) therapy.[1–3]

Airway oscillometry is an effort-independent tidal breathing manoeuvre that also assesses small airway function through measuring differences in resistance between 5 and 20 Hz (R5-R20), reactance at 5 Hz (X5) and area under reactance curve (AX).[4] It has previously been demonstrated that oscillometry BDR is related to asthma control,[5] and that R5-R20 and AX bronchodilator response display greater sensitivity compared to that of FEV_1 or FEF_{25-75} in response to salbutamol in mild to moderate asthma patients.[6] In this prospective cohort study, we aim to elucidate similarities and differences in BDR for spirometry and oscillometry in patients with poorly controlled severe asthma with type 2 inflammation.

Thirty-three severe asthma patients attending the Scottish Centre for Respiratory Research for screening into a separate clinical trial (EudraCT No. 2019–003763-22) were enrolled into this study between December 2020 and October 2021. Prior to their appointment, all patients were instructed to withhold their SABA for 6 h; ICS for 12 or 24 h depending on dosing frequency, long-acting beta-agonists (LABA) for 12 or 24 h; long-acting muscarinic antagonists (LAMA) for 12 or 24 h; theophylline for 48 h; leukotriene receptor antagonists (LTRA) for 48 h and antihistamines for 5 days. No patients were taking biologics at enrolment. Fractional exhaled nitric oxide (FeNO) was measured using NIOX VERO (Circassia) according to the manufacturer's instructions and ATS/ERS guidelines. Spirometry (Micromedical) was performed according to ERS guidelines. Thorasys TremoFlo Airwave Oscillometry system measurements were performed in triplicate to assess oscillometry according to the ERS guidelines with oscillometry always performed prior to spirometry. Blood testing was performed to detect levels of peripheral blood eosinophils (PBE) and circulating levels of specific IgE antibodies [Fluorescence enzyme-linked immunoassay (Phadia

Immunocap 250)] to defined common allergens including house dust mite, grass, cat, dog and silver birch. Asthma control was determined using the 6-point asthma control questionnaire (ACQ) and mini asthma quality of life questionnaire (mini-AQLQ). All patients were subsequently administered 400 μg of salbutamol via a pMDI through an aerochamber spacer device (Trudell Medical UK Ltd) with oscillometry and spirometry measurements repeated after 15 min. Statistical analysis was performed using SPSS version 27 and graphs were prepared with GraphPad Prism 6 (GraphPad Software Inc). Data were assessed for normality with Boxplots prior to analysis. Paired Student's T tests with a two tailed alpha error set at 0.05 were implemented to evaluate any significant differences in pulmonary function pre- and post-salbutamol. Independent Student's T tests were also used to compare pre-bronchodilator spirometry, oscillometry, type 2 biomarkers and ACQ in those patients with or without spirometry or oscillometry defined BDR. Pearson's correlation coefficients were computed to assess the relationship between percentage differences for spirometry and oscillometry. The standardized response mean (SRM) expresses the signal to noise ratio as mean change divided by SD (SRM ≥ 0.80 are considered highly sensitive). Ethical approval was obtained through the East of Scotland research ethics service.

The mean baseline demographic data were as follows: gender (F/M) 18/15; age 52 years; BMI: 31 kg/m^2; ACQ: 3.0; mini-AQLQ: 3.2; FEV_1: 76%; FEF_{25-75}: 39%; FVC: 98%; FEV_1/FVC: 0.63, R5: 0.59 kPa/L/s; R20: 0.40 kPa/L/s; R5-R20: 0.19 kPa/L/s; X5: −0.33 kPa/L/s; AX: 3.77 kPa/L; Fres: 24.00 Hz; PBE: 505 cells/μl; total IgE: 388 kU/L; neutrophils: 4586 cells/μl; FeNO: 54 ppb and number of positive specific IgE of 1. The mean ICS dose was 1875 μg; 79% were taking LABA; 52% LAMA; 64% LTRA; 21% theophylline; 70% oral antihistamine; 3% sodium cromoglicate; 48% intranasal steroids and 12% intranasal antihistamines. One patient was taking a daily oral prednisolone dose of 1 mg. Thirty-nine percent were ex-smokers with the remainder having never smoked.

When comparing pre- and post-bronchodilator measurements (Table 1), spirometry and oscillometry values were all statistically significant ($p < .001$). Similar outcomes resulted from repeating the analysis for those patients with AHR to mannitol ($n = 21$).

The greatest improvements after bronchodilation (expressed as % of baseline) were observed for R5-R20 (37.9%) and AX (53.5%) whilst the lowest improvements were demonstrated for FVC (4.1%) and FEV_1 (10.4%). SRMs for FEV_1, R5, X5, AX and F_{res} were all highly sensitive (>0.8) although was highest for FEV_1 (Table 1). Improvements in FEF_{25-75}% and R5-R20% were moderately correlated ($r = 0.47$; $p = .006$).

In our cohort of severe asthma patients, 11/33 (33%) had a positive BDR when using the standard FEV_1 criteria of >200ml and >12% improvement post-salbutamol. When using recently recommended oscillometry BDR criteria, namely R5 ≥ 29% or X5 ≥ 45%,[7] 12/33 (36%) had a positive BDR (Table 2). No significant differences in spirometry, oscillometry, asthma control or type 2 biomarkers were noted when using spirometry or oscillometry BDR criteria separately.

To our knowledge, this is the first study comparing BDR for oscillometry and spirometry in patients with poorly controlled severe asthma with type 2 inflammation. Respiratory impedance values for BDR in healthy volunteers have previously been

documented, but in contrast, our cohort of patients had evidence of severe asthma. Notably, the mean baseline FEV_1 improved by 231 ml and 10.4% pre- versus post-salbutamol. One possible explanation for the lack of spirometry BDR in this study perhaps could be related to the fact that severe asthma is more associated with airway remodelling and fixed airflow obstruction than mild-to-moderate asthma.[8]

Key messages

- FEF_{25-75} and oscillometry demonstrate greater percentage improvements in bronchodilator response than FEV_1 in moder severe asthma.
- Standardized response means for FEV_1 and oscillometry were highly sensitive.
- Oscillometry can be used as a viable alternative in patients unable to perform spirometry.

	Mean difference (95%CI)	% difference (95%CI)	p value	SRM
FEV_1 (L)	0.231 (0.295–0.168)	10.4 (13.2–7.5)	<.001	1.29
FEF_{25-75} (L/s)	0.356 (0.523–0.190)	25.9 (38–13.8)	<.001	0.76
FVC (L)	0.142 (0.219–0.066)	4.1 (6.2–1.9)	<.001	0.66
R5 (kPa/L/s)	0.12 (0.08–0.16)	20.1 (13.5–26.8)	<.001	1.07
R20 (kPa/L/s)	0.05 (0.02–0.07)	11.5 (5.8–17.1)	<.001	0.73
R5-R20 (kPa/L/s)	0.07 (0.05–0.10)	37.9 (24.4–51.5)	<.001	0.99
AX (kPa/L)	2.02 (1.16–2.87)	53.5 (30.8–76.2)	<.001	0.84
X5 (kPa/L/s)	0.11 (0.16–0.07)	33.7 (47.4–20)	<.001	
F_{res} (Hz)	4.60 (2.55–6.65)	19.5 (10.8–28.1)	<.001	0.90

TABLE 1 Mean absolute and percentage differences and standardized response means for pre- and post-bronchodilator oscillometry and spirometry measurements

Abbreviations: CI, confidence interval; SRM, standardized response means.

	FEV_1 BDR ($n = 11$) vs non-BDR ($n = 22$)	Oscillometry BDR ($n = 12$) vs non-BDR ($n = 21$)
FEV_1 (L)	2.24 vs. 2.23	2.40 vs. 2.14
FEF_{25-75} (L/s)	1.14 vs. 1.49	1.46 vs. 1.33
FVC (L)	3.85 vs. 3.34	3.82 vs. 3.33
R5 (kPa/L/s)	0.70 vs. 0.53	0.67 vs. 0.54
R20 (kPa/L/s)	0.45 vs. 0.38	0.42 vs. 0.40
R5-R20 (kPa/L/s)	0.25 vs. 0.16	0.25 vs. 0.15
AX (kPa/L)	5.03 vs. 3.14	5.02 vs. 3.05
X5 (kPa/L/s)	−0.37 vs. −0.32	−0.37 vs. −0.32
F_{res} (Hz)	26.16 vs. 23.04	27.47 vs. 22.16
ACQ	3.3 vs. 2.9	2.9 vs. 3.1
Mini AQLQ	3.1 vs. 3.2	3.4 vs. 3.1
FeNO (ppb)	74 vs. 40	45 vs. 55
PBE (cells/μl)	474 vs. 522	338 vs. 598*

TABLE 2 Comparisons of spirometry, oscillometry, asthma control and type 2 biomarkers according to presence or absence of bronchodilator response using FEV_1 or oscillometry criteria

Abbreviation: BDR, bronchodilator response; *$p < .05$.

One recent retrospective study observed that oscillometry BDR was associated with poor asthma control and was more sensitive than spirometry BDR.[9] However, this study did not investigate small airways resistance using R5-R20 or FEF_{25-75}. In this study, we have prospectively demonstrated that both reactance (X5 and AX) and resistance measurements (R5-R20) in addition to FEF_{25-75} showed the greatest improvements in BDR compared to FEV_1 (Table 1).

Improvements in FEF_{25-75}% and R5-R20% were moderately correlated. This is intuitive as both measurements are considered markers for SAD. Indeed, BDR values were highest for measurements of SAD including FEF_{25-75}, R5-R20, X5 and AX whilst FEV_1, FVC, R5, R20 and F_{res} had relatively lower BDR (Table 1). The findings from this study are clinically relevant as biologic therapy has previously been shown to improve FEF_{25-75} and R5-R20 in patients with severe asthma along with its well established effects on better asthma control.[4]

We appreciate our study is limited in terms of a relatively small sample size and results from a single Scottish centre and therefore larger multicentre studies are indicated to validate our results including patients taking biologics. However, this is the first prospective study to assess oscillometry BDR in severe asthma patients with type 2 inflammation and therefore we hope this novelty will lead to further studies in this rapidly evolving area.

In conclusion, measurements for small airways dysfunction including FEF_{25-75} and oscillometry demonstrated greater percentage improvements in bronchodilator response compared to baseline than FEV_1 and FVC in severe asthma patients. Standardized response means for FEV_1, R5, X5, AX and F_{res} were all highly sensitive although was highest for FEV_1.

AUTHORS CONTRIBUTION

Rory Chan and Brian J. Lipworth were both jointly responsible for idea conception and writing all versions of the manuscript. Rory Chan collected and analysed all data whilst Brian J. Lipworth provided overall supervision.

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CONFLICT OF INTEREST

Dr. Chan reports personal fees (talks) from AstraZeneca. Dr. Lipworth reports non-financial support (equipment) from GSK; grants, personal fees (consulting, talks and advisory board), other support (attending ATS and ERS) and from AstraZeneca, grants, personal fees (consulting, talks, advisory board), other support (attending ERS) from Teva, personal fees (consulting) from Sanofi, personal fees (consulting, talks and advisory board) from Circassia in relation to the submitted work; personal fees (consulting) from Lupin, personal fees (consulting) from Glenmark, personal fees (consulting) from Vectura, personal fees (consulting) from Dr Reddy, personal fees (consulting) from Sandoz; grants, personal fees (consulting, talks, advisory board), other support (attending BTS) from

Boehringer Ingelheim, grants and personal fees (advisory board and talks) from Mylan outside of the submitted work; and the son of BJL is presently an employee of AstraZeneca.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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