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## **Repeatability of impulse oscillometry in patients with severe asthma**

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Title: Repeatability of impulse oscillometry in patients with severe asthma

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## Abbreviations

ACQ	asthma control questionnaire
AERD	aspirin exacerbated respiratory disease
ATS	American thoracic society
AX	area under reactance curve
BDP	beclomethasone dipropionate
BMI	body mass index
BV	biological variability
CI	confidence interval
CRSwNP	chronic rhinosinusitis with nasal polyps
CV	coefficient of variation
ERS	European respiratory society
FEF <sub>25-75</sub>	forced expiratory flow between 25 and 75% of forced vital capacity
FeNO	fractional exhaled nitric oxide
FEV <sub>1</sub>	forced expiratory volume in 1 second
FVC	forced vital capacity
F <sub>res</sub>	resonance frequency
ICS	inhaled corticosteroid
IOS	impulse oscillometry
MCID	minimal clinically important difference
NHS	National Health Service
OCS	oral corticosteroid
PBE	peripheral blood eosinophils
R5	resistance at 5 Hz
R5-R20	difference between resistance at 5 and 20 Hz
R20	resistance at 20 Hz
SAD	small airways dysfunction

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Take home message: Repeatability of impulse oscillometry in severe asthma is unknown. We report on medium term repeatability for IOS and propose values for within subject biological variability in patients with poorly controlled severe asthma.

Impulse oscillometry (IOS) involves an effort independent tidal breathing manoeuvre to determine the presence or absence of small airways dysfunction (SAD), defined as raised peripheral airway resistance (difference in resistance between 5 and 20Hz (R5-R20)) and/or raised peripheral airway reactance (area under the reactance curve (AX)).(1) IOS has clear advantages over spirometry especially in patients where accurate forced volumetric measurements may be difficult or impossible to achieve, and has proven its utility in asthma and COPD although work is still required to determine normal reference ranges and the minimal clinically important difference (MCID) for changes in measurements.(2)

In medical statistics the coefficient of variation (CV) is commonly used as a measure of precision and repeatability of data and additionally can be utilised to assess variability between two different devices that perform the same task irrespective of their units of measurement.(3) CV is calculated by dividing the sample standard deviation by the sample mean and is usually expressed as a percentage. A larger CV value reflects higher variability and therefore lower consistency between repeated measurements in a given subject. Biological variability (BV), a measurement of natural fluctuation, can be calculated as the one sided 97.5% CI. Its value can be used as a surrogate for the minimal change that must be exceeded for a clinically significant treatment effect or MCID to occur.

Therefore, we performed a retrospective study to compare the within variability of IOS and spirometry measurements over two timepoints (T1 and T2) in 42 severe asthma patients attending our specialist NHS clinic who underwent no change in treatment over the period of assessment. Fractional exhaled nitric oxide (FeNO) was measured using NIOX VERO (Circassia, Oxford, UK) according to manufacturer's instructions and ATS/ERS guidelines.(4) Spirometry (Micromedical, Chatham, UK) was performed according to European Respiratory Society (ERS) guidelines.(5) IOS (Masterscreen, Carefusion Hoechberg, Germany) measurements were performed in triplicate according to the ERS guidelines with IOS always performed prior to spirometry.(1) Data were first analysed for normality using Boxplots and paired sample T tests were used to determine statistical significance with alpha error (two tailed) set at 0.05. Pearson's correlation coefficients were computed to assess the relationship between CVs for IOS and spirometry. Biological variability and coefficients of variation were calculated for each variable and the means (95% CI) presented in Table 1. The within subject absolute biological variability was calculated as a one sided 97.5%CI value. Other 95%CI were calculated as two-sided values. Caldicott Guardian approval was obtained prior to all data collection.

The mean baseline demographic data were as follows: gender (F/M) 27/15; age 53 years; ex-smoker 17%; current smoker 7%; FeNO 26ppb; peripheral blood eosinophils (PBE) 404 cells/ $\mu$ l; BMI 32kg/m<sup>2</sup>; FEV<sub>1</sub> 87%; FEF<sub>25-75</sub> 51%; FVC 106%; R5 0.55kPa/L/s (158% predicted); R20 0.42kPa/L/s (142% predicted); R5-R20 0.14kPa/L/s; AX 1.39kPa/L and resonance frequency, F<sub>res</sub> 17.61Hz. The percentage of patients taking long-acting beta agonist were 95%; long acting muscarinic antagonist 57%; leukotriene receptor antagonist 52%; theophylline 36%; oral antihistamine 60%; intranasal corticosteroids 55%; intranasal antihistamines 12%; anti-IgE therapy 5% and anti-IL5 therapy 12%. Our patients had preserved FEV<sub>1</sub> (mean %pred) but evidence of SAD as evidenced by reduced FEF<sub>25-75</sub> (%pred) but raised R5-R20 (kPa/L/s) and AX (kPa/L). Moreover, our severe asthma patients had a mean ACQ score of 2.1 and 4 asthma exacerbations requiring oral corticosteroids (OCS) in the past year denoting poor control despite a high beclomethasone dipropionate (BDP) equivalent ICS dose of 1,850 $\mu$ g. 6/42 (14%) patients had aspirin exacerbated respiratory disease (AERD) and 16/42 (38%) had chronic rhinosinusitis with nasal polyps (CRSwNP). The mean time in pulmonary function, ACQ score and FeNO between T1 and T2 was 321 days (SD 208; Range 63 - 1085). PBE counts were averaged over the preceding 6 months whilst FeNO results were obtained on the same day as pulmonary function and ACQ.

No statistically significant differences were detected when comparing spirometry, IOS, ACQ, PBE count or FeNO. Table 1 depicts the mean absolute and percentage changes with two-sided 95%CI, CVs with two-sided 95%CI and BVs with one sided 97.5%CI in pulmonary function. Spirometry as FEV<sub>1</sub>, FVC and FEF<sub>25-75</sub> had CVs ranging between 6.9% to 20.3%, whilst for IOS, CV values for R5, R20, F<sub>res</sub> and AX were between 12.9% to 39.2%. FEF<sub>25-75</sub> and AX had the highest CV values amounting to 20.3% and 39.2%. Differences in ACQ scores exceeded 0.5 in 71% of patients between T1 and T2. When repeating the analysis for patients with a baseline FEV<sub>1</sub><80% predicted (n=19), CV values were similar to the results of the overall analysis, and no significant differences in pulmonary function, ACQ or type 2 biomarkers were observed between T1 and T2. Analysis was repeated for patients who experienced a FEV<sub>1</sub> change of less than (n=22) or more than (n=20) the MCID of 230ml(6) respectively between T1 and T2 and for those with baseline IOS-defined SAD as R5-R20≥0.08kPa/L/s(7) (n=28) but no significant differences were observed. Weak correlations in variability were detected for FEF<sub>25-75</sub> with AX (r=0.37; p=0.015) and F<sub>res</sub> (r=0.35; p=0.025) between the two timepoints.

With regards to biological variability for AX, a one-sided 97.5%CI of 0.39 kPa/L infers that a change exceeding this is required to represent a clinically meaningful response. Notably, our CVs for FEV<sub>1</sub> (10.1%) and FEF<sub>25-75</sub> (20.3%) were comparable to that of previous literature.(8) This perhaps suggests that one should expect AX values to biologically vary more widely over time than R5, R20, F<sub>res</sub>, FEV<sub>1</sub> and FEF<sub>25-75</sub> even in the absence of treatment modification. A post-hoc analysis assessing the effect of propranolol and salbutamol on spirometry and IOS measurements demonstrated that AX had the largest magnitude of response with respect to bronchoconstriction and bronchodilation compared to R5, F<sub>res</sub>, FEV<sub>1</sub> and FEF<sub>25-75</sub>.(9) Previously we have also shown that IOS has greater sensitivity than spirometry for detecting bronchodilator response using 400µg albuterol in asthma patients.(10)

The within subject biological variability in ACQ was 0.6 units which is similar to the conventional MCID value of 0.5. Notably, the original paper by Juniper and colleagues(11) studied patients with relatively well controlled asthma and a mean ACQ < 1.5. One could perhaps postulate that in our cohort of asthma patients with severe uncontrolled disease and a higher mean ACQ of 2.1, a higher CV and BV could be expected. Hence the 97.5%CI values presented for spirometry and IOS could perhaps be interpreted as the change that must occur for a clinically meaningful improvement in severe asthma patients. Importantly, our BV values for FEV<sub>1</sub> and FVC align with current American Thoracic Society (ATS) and ERS spirometry repeatability guidelines advising measurements within ≤150ml should be achieved between manoeuvres.(12)

One prospective trial investigating IOS variability in adolescent asthma patients demonstrated significant day-to-day differences in R5, R5-R15 and AX, but not spirometry in children who were maintained on a stable treatment regimen.(13) A recent prospective study observed moderate concordance between FOT and spirometry values where the mean duration of time between measurements was 114 days in uncontrolled asthma patients taking a mean daily ICS dose of 1,015µg.(14) Another study(15) in clinically stable asthma patients found a moderate correlation between ACQ with spirometry and IOS measurements. We were therefore surprised that despite the majority of our patients undergoing a change in their ACQ score ≥0.5 no differences were observed in pulmonary function between T1 and T2. Once again, this could perhaps reflect a slightly different disease pattern associated with severe asthmatics where there could be a disconnect between asthma control and lung function.

To our knowledge, this is the first study comparing medium term variability in impulse oscillometry and spirometry measurements over time in severe asthma. We appreciate the limitations of our study including the small sample size along with results from a single Scottish Centre and therefore larger studies with more serial longitudinal measurements are required to validate our results. We also

appreciate there is a degree of uncertainty relating to disease control in our asthma patients over a relatively long duration (321 days) which could theoretically impact our results. Indeed, the wide range of intervals between the two evaluations is a significant limitation. However, the combination of no change in asthma therapy and no statistically significant or clinically relevant difference in FEV<sub>1</sub> between T1 and T2 might mitigate this possibility. One potential major limitation of our study was that patients were not precisely assessed between time point 1 and 2, and therefore this may be a source of possible bias. Although type 2 inflammatory biomarker results were only available in a subgroup of patients, PBE readings were intentionally averaged over the preceding 6 months due to significant temporal variability in severe asthma patients.(16)

In conclusion, we report on medium term repeatability for IOS and spirometry and propose values for within subject biological variability in patients with poorly controlled severe asthma.

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**Table 1 Mean absolute and percentage changes, coefficient of variation and biological variability in pulmonary function, ACQ and type 2 biomarkers between timepoints**

	<b>Mean absolute change (95% CI)</b>	<b>Mean percentage change (95% CI)</b>	<b>Mean CV (95% CI)</b>	<b>Biological Variability (97.5% CI)</b>
<b>FEV<sub>1</sub> (L)</b>	0.100 (-0.048 – 0.250)	4% (-2 – 10.1)	10.1% (6.7 – 13.5)	0.150
<b>FEF<sub>25-75</sub> (L/s)</b>	0.122 (-0.088 – 0.332)	6.9% (-5.2 - 19)	20.3% (14.1 – 26.5)	0.21
<b>FVC (L)</b>	0.118 (-0.026 – 0.261)	3.3% (-0.8 – 7.1)	6.9% (4.6 – 9.2)	0.15
<b>R5 (kPa/L/s)</b>	-0.01 (-0.07 – 0.06)	-1.8% (-12.7 – 10.9)	16.1% (11.6 – 20.6)	0.07
<b>R5-R20 (kPa/L/s)</b>	-0.02 (-0.06 – 0.02)	16.5% (-45.8 – 12.7)	33.1% (19.5 – 46.7)	0.04
<b>R20 (kPa/L/s)</b>	0.02 (-0.01 – 0.05)	4.8% (-2.4 – 11.9)	12.5% (9.2 – 15.8)	0.03
<b>AX (kPa/L)</b>	-0.17 (-0.55 – 0.22)	-12.2% (-39.6 – 15.8)	39.2% (28.9 – 49.6)	0.39
<b>F<sub>res</sub> (Hz)</b>	-0.11 (-1.61 – 1.39)	-0.6% (-9.1 – 7.9)	14% (9.4 – 18.5)	1.5
<b>ACQ</b>	-0.1 (-0.7 – 0.5)	5.7% (-35 – 23.6)	46.7% (30 – 63.3)	0.6
<b>PBE (cells/μL)*</b>	-35 (-138 – 69)	-8.8% (-35.1 – 17.5)	37.7% (25.1 – 50.3)	104
<b>FeNO (ppb)#</b>	-17 (-32 – -2)	-66.8 (-125.6 – -7.9)	43.7% (33 – 54.4)	15

*AX = area under the reactance curve; CV = coefficient of variation; FeNO = fractional exhaled nitric oxide; FEF<sub>25-75</sub> = forced mid expiratory flow rate between 25 and 75% of forced vital capacity (FVC); FEV<sub>1</sub> = forced expiratory volume in 1 second; F<sub>res</sub> = resonance frequency; PBE = peripheral blood eosinophils; R5 = resistance at 5Hz; R20 = resistance at 20Hz. Within subject biological variability was calculated as a one-sided 97.5%CI. Other 95%CI were two-sided. \*n=35 #n=25*