Repeatability of impulse oscillometry in patients with severe asthma

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To the Editor:

Impulse oscillometry (IOS) involves an effort-independent tidal breathing manoeuvre to determine the presence or absence of small airway dysfunction (SAD), defined as raised peripheral airway resistance (difference in resistance between 5 and 20 Hz (R_5–R_{20})) and/or raised peripheral airway reactance (area under the reactance curve (A_X)) [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% confidence interval. 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-subject variability of IOS and spirometry measurements over two timepoints (T1 and T2) in 42 severe asthma patients attending our specialist National Health Service clinic who underwent no change in treatment over the period of assessment. Fractional exhaled nitric oxide (F_{eNO}) was measured using NIOX VERO (Circassia, Oxford, UK) according to the manufacturer's instructions and American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines [4]. Spirometry (Micromedical, Chatham, UK) was performed according to ERS guidelines [5]. IOS (Masterscreen, Carefusion, Hoechberg, Germany) measurements were performed in triplicate according to 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. BV and CVs were calculated for each variable and the means (with 95% confidence intervals) presented in table 1. The within-subject absolute BV was calculated as a one-sided 97.5% confidence interval value. Other 95% confidence intervals 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 27 females and 15 males; age 53 years; ex-smokers 17%; current smokers 7%; F_{eNO} 26 ppb; peripheral blood eosinophils (PBE) 404 cells·μL^{-1}; BMI 32 kg·m^{-2}; forced expiratory volume in 1 s (FEV_1) 87%; forced vital capacity (FVC) 106%; forced expiratory flow between 25 and 75% of FVC ($FEF_{25–75}$) 51%; R_5 0.55 kPa·L^{-1}·s^{-1} (158% predicted); R_{20} 0.42 kPa·L^{-1}·s^{-1} (142% predicted); R_5–R_{20} 0.14 kPa·L^{-1}·s^{-1}; A_X 1.39 kPa·L^{-1} and resonance frequency, f_{res} 17.61 Hz. The percentage of patients taking long-acting beta-agonist was 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-IL-5 therapy 12%. Our patients had preserved FEV_1 (mean % pred) but evidence of SAD as evidenced by reduced $FEF_{25–75}$ (% pred) but raised R_5–R_{20} (kPa·L^{-1}·s^{-1}) and A_X (kPa·L^{-1}). Moreover, our severe asthma patients had a

Shareable abstract (@ERSpublications)
Repeatability of impulse oscillometry in severe asthma is unknown. This study reports on medium term repeatability for IOS and proposes values for within subject biological variability in patients with poorly controlled severe asthma. https://bit.ly/3a5o52W

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TABLE 1 Mean absolute and percentage changes, coefficient of variation (CV) and biological variability (BV) in pulmonary function, Asthma Control Questionnaire (ACQ) and type 2 biomarkers between timepoints

	Mean absolute change (95% CI)	Mean percentage change (95% CI)	Mean CV (95% CI)	BV (97.5% CI)
FEV_1 (L)	0.100 (−0.048–0.250)	4% (−2–10.1%)	10.1% (6.7–13.5%)	0.15
$FEF_{25–75}$ ($L \cdot s^{-1}$)	0.122 (−0.088–0.332)	6.9% (−5.2–19%)	20.3% (14.1–26.5%)	0.21
FVC (L)	0.118 (−0.026–0.261)	3.3% (−0.8–7.1%)	6.9% (4.6–9.2%)	0.15
R_5 ($kPa \cdot L^{-1} \cdot s^{-1}$)	−0.01 (−0.07–0.06)	−1.8% (−12.7–10.9%)	16.1% (11.6–20.6%)	0.07
$R_5–R_{20}$ ($kPa \cdot L^{-1} \cdot s^{-1}$)	−0.02 (−0.06–0.02)	16.5% (−45.8–12.7%)	33.1% (19.5–46.7%)	0.04
R_{20} ($kPa \cdot L^{-1} \cdot s^{-1}$)	0.02 (−0.01–0.05)	4.8% (−2.4–11.9%)	12.5% (9.2–15.8%)	0.03
A_X ($kPa \cdot L^{-1}$)	−0.17 (−0.55–0.22)	−12.2% (−39.6–15.8%)	39.2% (28.9–49.6%)	0.39
f_{res} (Hz)	−0.11 (−1.61–1.39)	−0.6% (−9.1–7.9%)	14% (9.4–18.5%)	1.5
ACQ	−0.1 (−0.7–0.5)	5.7% (−35–23.6%)	46.7% (30–63.3%)	0.6
PBE ($cells \cdot \mu L^{-1}$)[#]	−35 (−138–69)	−8.8% (−35.1–17.5%)	37.7% (25.1–50.3%)	104
F_{eNO} (ppb)[¶]	−17 (−32–−2)	−66.8% (−125.6–−7.9%)	43.7% (33–54.4%)	15

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25–75}$: forced mid-expiratory flow rate between 25 and 75% of FVC; R_5: resistance at 5 Hz; R_{20}: resistance at 20 Hz; A_X: area under the reactance curve; f_{res}: resonance frequency; PBE: peripheral blood eosinophils; F_{eNO}: fractional exhaled nitric oxide. Within subject BV was calculated as a one-sided 97.5% confidence intervals. Other 95% confidence intervals were two-sided. [#]: n=35; [¶]: n=25.

mean Asthma Control Questionnaire (ACQ) score of 2.1 and 4 asthma exacerbations requiring oral corticosteroids in the past year, denoting poor control despite a high beclomethasone diproprionate equivalent inhaled corticosteroid (ICS) dose of 1850 µg. 6/42 (14%) patients had aspirin-exacerbated respiratory disease and 16/42 (38%) had chronic rhinosinusitis with nasal polyps. The mean±SD time in pulmonary function, ACQ score and F_{eNO} measurements between T1 and T2 was 321±208 days (range 63–1085 days). PBE counts were averaged over the preceding 6 months whilst F_{eNO} 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 F_{eNO}. Table 1 depicts the mean absolute and percentage changes with two-sided 95% confidence intervals, CVs with two-sided 95% confidence intervals and BVs with one sided 97.5% confidence intervals in pulmonary function. For spirometry, FEV_1, FVC and $FEF_{25–75}$ had CVs ranging between 6.9% and 20.3%, whilst for IOS, CV values for R_5, R_{20}, f_{res} and A_X were between 12.9% and 39.2%. $FEF_{25–75}$ and A_X 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_1 <80% pred (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_1 change of less than (n=22) or more than (n=20) the MCID of 230 mL [6] between T1 and T2, and for those with baseline IOS-defined SAD as $R_5–R_{20}$ $\geqslant 0.08\ kPa \cdot L^{-1} \cdot s^{-1}$ [7] (n=28) but no significant differences were observed. Weak correlations in variability were detected for $FEF_{25–75}$ with A_X (r=0.37; p=0.015) and f_{res} (r=0.35; p=0.025) between the two timepoints.

With regards to BV for A_X, a one-sided 97.5% confidence interval of $0.39\ kPa \cdot L^{-1}$ infers that a change exceeding this is required to represent a clinically meaningful response. Notably, our CVs for FEV_1 (10.1%) and $FEF_{25–75}$ (20.3%) were comparable to that of previous literature [8]. This perhaps suggests that one should expect A_X values to biologically vary more widely over time than R_5, R_{20}, f_{res}, FEV_1 and $FEF_{25–75}$, 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 A_X had the largest magnitude of response with respect to bronchoconstriction and bronchodilation compared to R_5, f_{res}, FEV_1 and $FEF_{25–75}$ [9]. Previously we have also shown that IOS has greater sensitivity than spirometry for detecting bronchodilator response using 400 µg albuterol in asthma patients [10].

The within-subject BV in ACQ was 0.6 units, which is similar to the conventional MCID value of 0.5. Notably, the original paper by JUNIPER *et al.* [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% confidence interval 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_1 and FVC align with current ATS and ERS spirometry repeatability guidelines advising measurements within ⩽150 mL should be achieved between manoeuvres [12].

One prospective trial investigating IOS variability in adolescent asthma patients demonstrated significant day-to-day differences in R_5, R_5–R_{15} and A_X, but not spirometry in children who were maintained on a stable treatment regimen [13]. A recent prospective study observed moderate concordance between forced oscillation technique 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 1015 µg [14]. Another study in clinically stable asthma patients found a moderate correlation between ACQ with spirometry and IOS measurements [15]. 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 IOS 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_1 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 BV in patients with poorly controlled severe asthma.

Rory Chan, Rasads Misirovs and Brian Lipworth

Scottish Centre for Respiratory Research, School of Medicine, University of Dundee, Ninewells Hospital, Dundee, UK.

Corresponding author: Brian Lipworth (b.j.lipworth@dundee.ac.uk)

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