

Between-visit variability of small airway obstruction markers in patients with asthma

To the Editor:

Clinical trials in patients with airway diseases often use forced expiratory volume in 1 s (FEV₁) as the sole physiological outcome measure. However, FEV₁ is thought to be insensitive to obstruction of the smaller airways, which may be particularly relevant in asthma [1]. Putative markers of small airway obstruction include measures of airway resistance using impulse oscillometry (IOS) [2] and indices of ventilation heterogeneity derived from multiple-breath inert gas washout (MBW) [3]. We recently showed that increased airway resistance at 5 Hz (*R*₅) and 20 Hz (*R*₂₀) is associated with worse asthma control and more frequent exacerbations [4], and FARAH *et al.* [5] demonstrated that MBW parameters may be responsive to asthma therapy.

In order to conduct clinical trials using these alternative outcome measures, it is necessary to be assured of their repeatability and stability over time. Moreover, an estimate of between-visit variability in the stable state is required so that sample size calculations can be performed. We therefore aimed to determine the between-visit variability of a range of IOS and MBW indices in a group of patients with asthma in the stable state. We investigated between-visit variability over two time intervals, namely 2 weeks and 3 months, in order to encompass the typical lengths of treatment period that are used in clinical trials.

We recruited 18 adults (age >18 years) with moderate-to-severe asthma (Global Initiative for Asthma treatment steps 3–5 [6]), diagnosed by a specialist asthma physician in a secondary care setting, according to British Thoracic Society guidelines [7]. The study was approved by the National Research Ethics Committee – East Midlands Leicester, and all participants gave their written informed consent. The participant group comprised nine males and nine females with a mean \pm SD age of 58 ± 11 years. All participants were treated with inhaled corticosteroids (1000–2000 μ g per day, beclomethasone dipropionate equivalent) and long-acting β_2 -agonists. 11 patients received maintenance low-dose prednisolone (5–15 mg per day). Post-bronchodilator FEV₁ was $80.5 \pm 23.0\%$ predicted with bronchodilator reversibility of $13.5 \pm 16.0\%$. A previous history of atopy was documented in nine patients. Geometric mean (95% CI) sputum eosinophil fraction was 2.6% (1.1–6.3%) and the neutrophil fraction was $58.6 \pm 28.2\%$.

At each study visit, participants completed the six-point Asthma Control Questionnaire [8]. Following administration of a bronchodilator (salbutamol 400 μ g *via* a metered-dose inhaler and spacer), IOS, MBW and spirometry were performed at baseline, then at 2 weeks and 3 months following baseline. All study visits took place in the stable state ≥ 6 weeks following any exacerbation of asthma.

IOS was performed using a Jaeger MasterScreen Impulse Oscillometry System (Viasys Healthcare GmbH, Hoechberg, Germany) according to standard guidelines [9]. Participants wore a nose clip and supported their cheeks while an impulse waveform was delivered to their respiratory system *via* a loudspeaker connected to a mouthpiece, during relaxed tidal breathing. Each test lasted 60 s, with an impulse frequency of 5 Hz, and was repeated in triplicate. The mean value from the triplicate tests was recorded for each IOS parameter.

MBW was performed in triplicate according to current guidelines [3], using the sulfur hexafluoride wash-in method described by HORSLEY *et al.* [10]. Participants wore a nose clip and breathed an air mixture containing 0.2% sulfur hexafluoride, while maintaining a steady respiratory rate of ~ 12 breaths per minute and a constant tidal volume of 1 L, using a real-time visual display of inspired volume as a guide. Respiratory flows and exhaled breath sulfur hexafluoride concentrations were monitored using an Innocor photoacoustic gas analyser (Innovision A/S, Odense, Denmark). Once inhaled and exhaled sulfur hexafluoride concentrations had equalised, participants were switched to breathing room air during an expiration and continued breathing at the same respiratory rate and tidal volume. The test was terminated once the end-tidal concentration of sulfur hexafluoride in exhaled breath fell below 1/40th of the original concentration for three consecutive breaths. Lung clearance index (LCI) [3], *S*_{cond} (conductive ventilation heterogeneity) and *S*_{acin} (acinar ventilation heterogeneity) [11] were calculated using custom software written with TestPoint (Measurement Computing Corporation, Norton, MA, USA).

The intraclass correlation coefficient (ICC) (SPSS Version 20; IBM Corporation, Somers, NY, USA) was calculated for each physiological variable, for the 2-week and 3-month time intervals (table 1). Between-visit repeatability was good at both time intervals for most IOS and MBW parameters, with ICC values >0.8 in the majority of cases. However, the repeatability of *Scond* and *Sacin* at 3 months was only moderate, with ICC values of 0.63 and 0.71 respectively. Within-visit repeatability was also assessed using the ICC of triplicate tests performed at baseline. All physiological measurements had high within-visit repeatability (ICC >0.85), with the exception of *Scond*. Previous investigators have also noted the poor within-visit repeatability of *Scond* [12], suggesting that this parameter may be less suitable than LCI and *Sacin* as an outcome measure in clinical trials.

The mean, standard deviation and 95% confidence intervals of between-visit differences are shown in table 1. The standard deviation data may be used, in conjunction with estimates of the minimal clinically important difference (MCID), to perform sample size calculations for interventional studies in patients with asthma. Given a parallel group study design in which the change in the variable of interest from baseline to follow-up is compared between an intervention and a control group using a parametric test, the required sample size may be calculated using a standard formula [13]. Although the MCID has not been established for most small airway outcome measures, estimates can be made from previously published data. YAMAGUCHI *et al.* [14] compared the response to small-particle and standard corticosteroid inhalers in steroid-naïve asthmatics using IOS. They observed a reduction in *R5* minus *R20* of $0.05 \text{ kPa}\cdot\text{L}^{-1}\cdot\text{s}$ in the small-particle group and $0.02 \text{ kPa}\cdot\text{L}^{-1}\cdot\text{s}$ in the standard group, thus giving a difference between groups of $0.03 \text{ kPa}\cdot\text{L}^{-1}\cdot\text{s}$ with respect to the change in *R5-R20* from baseline to follow-up. The sample size required to detect this difference following a 2-week treatment period with 80% power and 5% two-tailed significance would be 28 per treatment arm, which would be feasible in most clinical trial settings.

A potential limitation of our study was the relatively high mean age of our participants. It is possible that younger patients with asthma manifest a greater degree of variability in airway function than older patients, and further studies are required to investigate this possibility. However, the relative preponderance of middle-aged patients in our participant group is typical of previously described refractory asthma cohorts [15], and is thus representative of patients most likely to be enrolled in clinical trials. As expected, variability was greater at 3 months than at 2 weeks for most outcome measures. However, LCI was a notable exception to this pattern. We therefore recommend that the 2-week estimate of variability be used for all sample size calculations involving LCI, in order to mitigate the risk of the study being underpowered.

We conclude that IOS parameters are stable over time and have potential as outcome measures in clinical asthma trials. MBW indices are moderately stable but require further investigation in patients with asthma. Further studies are required to determine the longer-term variability of MBW and IOS parameters, as well as to establish the MCID for a number of small airway outcome measures.

TABLE 1 Between-visit variability of physiological variables in patients with asthma

	Baseline values		Variability at 2 weeks		Variability at 3 months	
	Mean \pm SD	ICC [#]	Mean \pm SD change from baseline (95% CI)	ICC [†]	Mean \pm SD change from baseline (95% CI)	ICC [†]
ACQ-6 score	1.61 \pm 1.14		0.02 \pm 0.64 (-1.24–1.28)	0.83	0.04 \pm 0.85 (-1.63–1.71)	0.78
FEV1 L	2.21 \pm 0.82	0.99	-0.04 \pm 0.14 (-0.32–0.24)	0.98	0.04 \pm 0.18 (-0.33–0.40)	0.98
MEF50 L·s ⁻¹	2.51 \pm 1.55	0.98	-0.15 \pm 0.50 (-1.13–0.82)	0.94	-0.07 \pm 0.58 (-1.20–1.06)	0.94
R5 kPa·L ⁻¹ ·s	0.52 \pm 0.18	0.94	-0.02 \pm 0.08 (-0.18–0.14)	0.89	-0.02 \pm 0.09 (-0.21–0.16)	0.86
R20 kPa·L ⁻¹ ·s	0.39 \pm 0.12	0.90	-0.01 \pm 0.06 (-0.12–0.10)	0.88	-0.02 \pm 0.06 (-0.14–0.10)	0.85
R5-R20 kPa·L ⁻¹ ·s	0.14 \pm 0.10	0.97	-0.02 \pm 0.04 (-0.09–0.06)	0.91	-0.01 \pm 0.05 (-0.12–0.10)	0.84
X5 kPa·L ⁻¹ ·s	-0.19 \pm 0.11	0.94	0.02 \pm 0.05 (-0.08–0.11)	0.88	0.03 \pm 0.06 (-0.08–0.15)	0.80
Ax kPa·L ⁻¹	1.47 \pm 1.42	0.98	-0.25 \pm 0.59 (-1.40–0.91)	0.88	-0.23 \pm 0.67 (-1.54–1.09)	0.86
LCI	8.20 \pm 1.48	0.95	0.14 \pm 1.04 (-1.89–2.18)	0.78	-0.25 \pm 0.63 (-1.48–0.99)	0.91
Scond L ⁻¹	0.066 \pm 0.081	0.23	0.004 \pm 0.038 (-0.072–0.079)	0.89	-0.007 \pm 0.057 (-0.119–0.104)	0.63
Sacin L ⁻¹	0.207 \pm 0.127	0.87	-0.024 \pm 0.067 (-0.156–0.108)	0.83	-0.027 \pm 0.068 (-0.16–0.11)	0.71

ICC: intraclass correlation coefficient; ACQ-6: six-point Asthma Control Questionnaire; FEV1: forced expiratory volume in 1 s; MEF50: midexpiratory flow at 50% of vital capacity; R5: resistance at 5 Hz; R20: resistance at 20 Hz; R5-R20: resistance at 5 Hz minus resistance at 20 Hz; X5: reactance at 5 Hz; Ax: reactance area; LCI: lung clearance index; Scond: conductive ventilation heterogeneity; Sacin: acinar ventilation heterogeneity. #: of triplicate tests performed at baseline; †: of tests performed at baseline versus follow-up visits.



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Small airway obstruction markers are stable over time and have potential as outcome measures in clinical trials <http://ow.ly/tCzp2>

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Bronchial obstruction and reversibility in children: inspiratory or expiratory resistance?

To the Editor:

Assessing bronchial obstruction and reversibility is of help in diagnosing asthma. The forced oscillation technique (FOT) has gained popularity in children since minimal cooperation is required. Owing to the fact