Long-term variability of oscillatory impedance in stable obstructive airways disease

Received: 21 Sept 2020
Accepted: 1 March 2021

To the Editor:

Respiratory oscillometry (or forced oscillation technique (FOT)), measures the mechanical properties of the respiratory system by superimposing oscillatory pressure waves at the mouth during quiet tidal breathing. Parameters include respiratory system resistance (R_{rs}), a measure of airway calibre, and reactance (X_{rs}), representing the elastic and inertive properties which are sensitive to airway closure [1]. FOT is increasingly being used for clinical monitoring of airways disease, which complements spirometric function [2].

Oscillometry parameters correlate well with symptoms and quality of life in asthma and COPD [3–6], and changes in X_{rs} correlate with clinical improvement during recovery from acute COPD exacerbations [7]. Furthermore, oscillometry may be more sensitive than spirometry in detecting bronchodilator responses in asthma and smoking-related changes in lung function of healthy smokers [5, 8, 9]. Following allogeneic haemopoietic stem-cell transplantation (allo-HSCT), oscillometric conductance is altered, which may reflect altered lung–airway interactions [10]; oscillometry may also prove useful for detecting bronchiolitis obliterans syndrome (BOS) in these patients.

Despite being an emerging clinical test, the minimal clinically important difference (MCID) for FOT remains uncertain. While the short-term variability in R_{rs} and X_{rs} is known [11, 12], longer-term variability is not. Knowing their variations between routine clinic visits in clinically stable patients is essential to estimate what are clinically important changes over time. Therefore, our aim in this study was to determine the variability in oscillometric parameters between clinic visits over weeks or months, in three patient groups during a period of clinical stability (allo-HSCT recipients without BOS, asthma patients and COPD patients) and in healthy subjects.

Longitudinal lung function data from patients who attended tertiary airway clinics were reviewed. Patients were included if they had three or more clinic visits between 1 January 2015 and 1 May 2020, in which spirometry and FOT were performed during a clinically stable period. Only data recorded from the first three visits were used. Stability was defined by clinician assessment: no change in symptoms, no respiratory infection in the past 6 weeks and no changes in treatment. Allo-HSCT recipients with BOS or pre-stage BOS (BOS-0p), as defined by the National Institutes of Health consensus guidelines [13], were excluded. Sample size was determined by availability of data from these opportunistic patient groups. Patients with asthma had a physician-diagnosis of asthma and were current nonsmokers with a smoking history of <10 pack-years. COPD patients had a physician-diagnosis of COPD, >10 pack-year smoking history, and post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio below the lower limit of normal. Healthy participants were current nonsmokers with a smoking history of <10 pack-years and no respiratory disease and underwent repeated FOT and spirometry measurements ⩾6 weeks apart; half were FOT-naïve.

Oscillometry was performed using the TremoFlo C-100 device (Thorasys, Thoracic Medical Systems) according to European Respiratory Society (ERS) recommendations [1]. At each visit, 30 s recordings were acquired in triplicate and at least three artefact-free breaths per recording were required for technical acceptability. Resistance and reactance at 5 Hz were examined as means of the entire 30 s recording (R_{rs5} and X_{rs5}), or of the inspiratory portions of the breaths ($R_{rsinsp5}$ and $X_{rsinsp5}$, respectively). Frequency

Shareable abstract (@ERSpublications)
FOT parameters have good long-term repeatability in patients with stable obstructive airways disease, facilitating its ability to detect sensitive changes in airways disease. Novel cut-off values presented may help determine clinically significant change. https://bit.ly/3emL7FI

Cite this article as: Rutting S, Badal T, Wallis R, *et al*. Long-term variability of oscillatory impedance in stable obstructive airways disease. *Eur Respir J* 2021; 58: 2004318 [DOI: 10.1183/13993003.04318-2020].

dependence of R_{rs} (R_{rs} at 5 Hz minus R_{rs} at 19 Hz (R_{rs5-19})) and the inspiratory minus expiratory difference in X_{rs5} ($X_{rs5insp-exp}$) were also examined. All reported parameters were calculated as the mean of three technically acceptable measurements.

Between-visit variability was expressed as the standard deviation (SD_{bv}), the coefficient of variation (CoV) calculated as the ratio of the SD_{bv} to the mean and intraclass correlation coefficient (ICC; mixed-effects model, absolute agreement, mean of three raters, using SPSS (v26; IBM)) of mean FOT measurements of three separate clinic visits. In addition, we calculated the coefficient of repeatability (CoR), defined as twice the standard deviation of the differences between two pairs of consecutive clinic visits from three clinical visits per patient. In the asthma and COPD groups, only post-bronchodilator measurements were used.

31 healthy subjects, 23 allo-HSCT recipients and 53 asthma and 36 COPD patients (n=8 Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1; n=12 GOLD stage 2; n=15 GOLD stage 3; and n=1 GOLD stage 4) were included. Healthy participants had a median (interquartile range (IQR)) age of 37.0 (30.0–50.0) years and were younger than COPD (69.5 (62.0–75.0) years) and asthmatic (67.0 (50.5–75.0) years) patients ($p<0.0001$ for both). Allo-HSCT recipients were aged 55.0 (49.0–63.0) years and were younger than COPD participants ($p=0.002$). The COPD and asthmatic participants had airway obstruction (FEV_1/FVC ratio z-scores <-1.64) and higher R_{rs5} and more negative X_{rs5} compared to the healthy group ($p<0.0001$). There was a range of abnormalities in airway obstruction and airway mechanics in the asthma and COPD groups, but overall the COPD group had more severe airway obstruction (mean±SD FEV_1/FVC z-score −3.49±1.10 and FEV_1 53.4±19.8% predicted) and more abnormal X_{rs5} (mean z-score −3.35±2.34) than the asthmatic cohort (mean FEV_1/FVC z-score, FEV_1 and X_{rs5} z-scores −1.40±1.98, 75.4±18.6% pred and −1.64±2.19, respectively; $p<0.01$). Spirometric and FOT measures were within normal limits and not different between the healthy and allo-HSCT participants.

Between-visit variability (SD_{bv}) of all FOT parameters was higher in asthma and COPD compared to health (table 1). However, SD_{bv} of all FOT parameters were comparable between allo-HSCT and health, and between asthma and COPD. Between-visit variability relative to the mean (CoV) for all FOT parameters were comparable between the four groups (*e.g.* CoV for R_{rs5} was 7.8% (4.8–12.6%), 12.3% (6.7–16.3%), 11.1% (6.4–16.4%) and 11.1% (6.4–14.0%) in health, allo-HSCT, asthma and COPD, respectively). The high-to-excellent ICC values (>0.85) of R_{rs5}, $R_{rsinsp5}$, X_{rs5} and $X_{rsinsp5}$ in each group indicate that they are highly repeatable measures, despite the wide range of R_{rs5} and X_{rs5} across the cohorts. The ICC of R_{rs5-19} and $X_{rs5insp-exp}$ were also high in the healthy, asthma and COPD groups, but were lower in the allo-HSCT group, indicating their higher within-subject variability.

Several studies have examined within-day, day-to-day or week-to-week repeatability of R_{rs5} and X_{rs5} in adults and children with and without airways disease [11, 12, 14–16], and also demonstrated high (>0.80) ICC values [11, 15]. However, these studies may not be generalisable to the clinical setting, in which stable patients are typically assessed several months apart. The FOT measurement repeatability between clinic visits in the present study is a representation of real-world behaviour of these parameters. The median (IQR) time between first and third visit was 10.0 (4.0–15.0) months, 9.0 (6.0–13.0) months, 14.0 (10.0–21.0) months and 16.5 (9.3–20.8) months in health, allo-HSCT, asthma and COPD, respectively. The median (IQR) time between two consecutive visits was 5.5 (2.0–7.5) months in the healthy group, 4.5 (3.0–6.5) months in the allo-HSCT group, 7.5 (5.0–10.5) months in the asthma group and 8.2 (4.5–10.3) months in the COPD group, with the interval being greater in COPD compared to allo-HSCT ($p=0.005$) and healthy groups ($p=0.01$). However, between-visit intervals were unrelated to between-visit variability (SD_{bv}) of all FOT parameters in all groups. Between visits 1 and 3, there were significant decreases [12] in X_{rs5} in 13 out of 53 asthmatic participants and 12 out of 36 COPD participants (although only in three in R_{rs5} in asthma and three in COPD). Thus, in these participants, some of the variability may be related to progressive decline.

The CoR data during a period of stable disease for the three patient groups (table 1) are novel. We show that variations in R_{rs5} up to 33% in asthma and COPD are typical of stable patients, while variations in X_{rs5} up to 64% in asthma and 55% COPD can be present. The larger variability in X_{rs5} compared to R_{rs5} has been consistently reported and this may have implications for defining an appropriate threshold or MCID. Oostveen *et al.* [12] reported short-term CoRs of 17.4% and 36.7% for R_{rs5} and X_{rs5}, respectively, in healthy participants measured 15 min apart, which mostly represents the technical variability of the test. The higher CoRs reported in the current present study of 30% and 54% probably represent both test variability as well as natural physiological variability over months. The relative CoRs for FOT were more variable than for spirometry, but importantly, the ICCs were similar, suggesting similar potential clinical utility. This may be explained by tidal breathing *versus* a maximal "best" effort test, and because in health,

TABLE 1 Baseline data taken from the first visit for each cohort

	Baseline values	Change over two consecutive visits (CoR absolute/relative)	SD_{bv}	ICC
Health (n=31)				
FEV_1 L	3.54 (2.94–4.06)	−0.02±0.16 (0.32/8%)	0.07 (0.04–0.13)	0.99
R_{rs5} $cmH_2O{\cdot}s{\cdot}L^{-1}$	2.88 (2.15–3.21)	0.06±0.45 (0.90/30%)	0.19 (0.10–0.32)	0.94
X_{rs5} $cmH_2O{\cdot}s{\cdot}L^{-1}$	−0.99 (−0.72– −1.34)	−0.03±0.26 (0.53/54%)	0.13 (0.09–0.17)	0.93
$R_{rsinsp5}$ $cmH_2O{\cdot}s{\cdot}L^{-1}$	2.73 (2.06–3.18)	0.07±0.34 (0.68/25%)	0.18 (0.10–0.35)	0.94
$X_{rsinsp5}$ $cmH_2O{\cdot}s{\cdot}L^{-1}$	−1.16 (−0.91– −1.64)	−0.03±0.30 (0.61/52%)	0.14 (0.07–0.22)	0.94
R_{rs5-19} $cmH_2O{\cdot}s{\cdot}L^{-1}$	0.19 (−0.04–0.34)	−0.01±0.19 (0.40)	0.11 (0.07–0.14)	0.89
$X_{rs5insp-exp}$ $cmH_2O{\cdot}s{\cdot}L^{-1}$	−0.38 (−0.45–0.20)	0.03±0.19 (0.40)	0.12 (0.07–0.18)	0.89
Allo-HSCT (n=23)				
FEV_1 L	3.41 (2.80–3.84)	−0.01±0.22 (0.45/13%)	0.12 (0.05–0.21)	0.98
R_{rs5} $cmH_2O{\cdot}s{\cdot}L^{-1}$	2.65 (2.12–3.96)	0.04±0.54 (1.08/32%)	0.30 (0.16–0.41)	0.94
X_{rs5} $cmH_2O{\cdot}s{\cdot}L^{-1}$	−1.08 (−0.77– −1.30)	−0.01±0.37 (0.74/54%)	0.19 (0.05–0.28)	0.85
$R_{rsinsp5}$ $cmH_2O{\cdot}s{\cdot}L^{-1}$	2.35 (2.04–2.88)	0.01±0.50 (1.00/34%)	0.17 (0.12–0.32)	0.96
$X_{rsinsp5}$ $cmH_2O{\cdot}s{\cdot}L^{-1}$	−1.23 (−0.87– −1.55)	0.01±0.44 (0.88/49%)	0.18 (0.05–0.28)	0.89
R_{rs5-19} $cmH_2O{\cdot}s{\cdot}L^{-1}$	0.05 (−1.00–0.61)	0.01±0.33 (0.67)	0.16 (0.10–0.27)	0.69
$X_{rs5insp-exp}$ $cmH_2O{\cdot}s{\cdot}L^{-1}$	−0.33 (−0.58–0.17)	0.05±0.55 (1.10)	0.11 (0.06–0.33)	0.54
Asthma (n=53)				
FEV_1 L	2.07 (1.53–2.53)$^{\#,\P}$	0.03±0.19 (0.38/21%)	0.09 (0.05–0.14)	0.99
R_{rs5} $cmH_2O{\cdot}s{\cdot}L^{-1}$	3.84 (3.14–5.02)$^{\#,\P}$	0.06±0.72 (1.44/33%)	0.37 (0.22–0.59)$^{\#}$	0.95
X_{rs5} $cmH_2O{\cdot}s{\cdot}L^{-1}$	−1.61 (−1.17– −2.88)$^{\#,\P}$	0.04±1.14 (2.28/64%)	0.30 (0.15–0.56)$^{\#,\P}$	0.94
$R_{rsinsp5}$ $cmH_2O{\cdot}s{\cdot}L^{-1}$	3.51 (2.95–4.25)$^{\#,\P}$	0.09±0.72 (1.44/34%)	0.32 (0.16–0.55)$^{\#}$	0.92
$X_{rsinsp5}$ $cmH_2O{\cdot}s{\cdot}L^{-1}$	−1.98 (−1.42– −2.85)$^{\#,\P}$	−0.05±0.64 (1.28/62%)	0.28 (0.15–0.42)$^{\#,\P}$	0.91
R_{rs5-19} $cmH_2O{\cdot}s{\cdot}L^{-1}$	0.50 (0.27–1.45)$^{\#,\P}$	0.02±0.52 (1.04)	0.22 (0.14–0.37)$^{\#}$	0.92
$X_{rs5insp-exp}$ $cmH_2O{\cdot}s{\cdot}L^{-1}$	−0.27 (−0.56–0.16)	−0.13±1.68 (3.36)	0.30 (0.18–0.68)$^{\#,\P}$	0.89
COPD (n=36)				
FEV_1 L	1.35 (1.07–2.06)$^{+,\S}$	0.05±0.13 (0.26/20%)	0.08 (0.06–0.15)	0.99
R_{rs5} $cmH_2O{\cdot}s{\cdot}L^{-1}$	4.37 (3.49–5.26)$^{+,\S}$	0.00±0.89 (1.78/33%)	0.36 (0.25–0.57)$^{+}$	0.91
X_{rs5} $cmH_2O{\cdot}s{\cdot}L^{-1}$	−3.48 (−1.62– −5.54)$^{+,\S}$	0.25±1.17 (2.34/55%)	0.54 (0.23–1.16)$^{+,\S}$	0.95
$R_{rsinsp5}$ $cmH_2O{\cdot}s{\cdot}L^{-1}$	4.01 (3.16–4.83)$^{+,\S}$	0.06±0.73 (1.46/32%)	0.31 (0.20–0.61)$^{+}$	0.91
$X_{rsinsp5}$ $cmH_2O{\cdot}s{\cdot}L^{-1}$	−2.39 (−1.46– −3.14)$^{+,\S}$	0.03±0.58 (1.16/47%)	0.31 (0.15–0.55)$^{+,\S}$	0.94
R_{rs5-19} $cmH_2O{\cdot}s{\cdot}L^{-1}$	1.48 (0.94–2.04)$^{+,\S,f}$	−0.02±0.75 (1.50)	0.24 (0.15–0.47)$^{+}$	0.88
$X_{rs5insp-exp}$ $cmH_2O{\cdot}s{\cdot}L^{-1}$	1.74 (−0.11–3.46)$^{+,\S,f}$	−0.32±1.59 (3.18)	0.68 (0.26–1.62)$^{+,\S}$	0.93

Data are presented as median (interquartile range) or mean±SD, unless otherwise stated. Between-visit variability is expressed as coefficient of repeatability (CoR), calculated as 2 SD of the difference in mean forced oscillation technique (FOT) measurements between two consecutive visits and is expressed as absolute ($cmH_2O{\cdot}s{\cdot}L^{-1}$) and relative (%) terms, from the three clinic visits were used to calculate CoRs. In addition, variability was expressed as between-visit standard deviation (SD_{bv}) of three mean FOT measurements of three separate clinic visits. The intraclass correlation coefficient (ICC) was calculated using a mean-rating two-way mixed-effects model with absolute agreement. For asthmatic and COPD subjects, post-bronchodilator measurements are used to calculate variability. Comparison between groups were made using a Kruskal–Wallis test with a Bonferroni *post hoc* test. FEV_1: forced expiratory volume in 1 s; R_{rs5}: respiratory system resistance at 5 Hz; X_{rs5}: respiratory system reactance at 5 Hz; $R_{rsinsp5}$: R_{rs5} for inspiration only; $X_{rsinsp5}$: X_{rs5} for inspiration only; R_{rs5-19}: respiratory system resistance at 5 Hz minus respiratory system resistance at 19 Hz; $X_{rs5insp-exp}$: X_{rs5} during inspiration minus X_{rs5} during expiration; allo-HSCT: allogeneic haemopoietic stem-cell transplantation. $^{\#}$: p<0.05 normal *versus* asthma; ¶: p<0.05 allo-HSCT *versus* asthma; $^{+}$: p<0.05 normal *versus* COPD; §: p<0.05 allo-HSCT *versus* COPD; ^{f}: p<0.05 asthma *versus* COPD.

spirometry is larger (hence lower relative CoR) whereas R_{rs} and X_{rs} have smaller absolute values (hence greater relative CoR).

These variability measures are based on clinical assessment without lung function. When we included ⩽15% change in FEV_1 between two consecutive visits as a criterion of stability [17], variability decreased marginally: CoRs for R_{rs5} and X_{rs5} were 1.44 (32%) and 2.14 (61%), respectively, in asthma (n=45) and 1.80 (33%) and 2.22 (52%), respectively, in COPD (n=30). Correspondingly, the median (IQR) SD_{bv} of R_{rs5} and X_{rs5} were 0.34 (0.21–0.56) and 0.25 (0.14–0.44), respectively in asthma and 0.34 (0.24–0.51) and 0.47 (0.17–0.76), respectively in COPD.

A potential limitation of this study is that the groups were not matched for age or gender. However, neither were related to between-visit standard deviation and were unlikely to have influenced the results, consistent with other studies [16]. Additionally, due to practical reasons, most participants did/could not withhold bronchodilator medications according to the recommended ERS/American Thoracic Society bronchodilator

withholding times. Inhaled medications were taken at variable times prior to testing at each visit. To mitigate any potential confounding, we used the post-bronchodilator measurements in asthma and COPD patients. Thus, the variability reported for these patients and any differences between groups may be underestimated; however, it is more representative of their real-world scenario. It also includes any possible variability in the bronchodilator response itself, particularly in asthma.

In summary, this study demonstrates that FOT parameters have good long-term repeatability as shown by high ICC values in health and in allo-HSCT, asthma and COPD, but also that variability differs between diseases, probably due to differences in baseline values. The reported cut-off values for between-visit variation in the three groups will help determine thresholds for MCIDs to detect increased disease activity, progression or positive treatment responses, as well as inform power calculations for clinical studies using oscillometry. These findings also help interpretation of longitudinal FOT measurements in the clinical setting.

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Data availability: The datasets generated and/or analysed during the study are available from the corresponding author on reasonable request.

Conflict of interest: S. Rutting has nothing to disclose. T. Badal has nothing to disclose. R. Wallis has nothing to disclose. R.E. Schoeffel has nothing to disclose. N. Roche has nothing to disclose. A.M. Cottee has nothing to disclose. D.G. Chapman has nothing to disclose. M. Greenwood has nothing to disclose. C.S. Farah has nothing to disclose. G.G. King has received consultancy fees for talks, chairmanship, advisory boards and conference sponsorship/attendance from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini, MundiPharma and Novartis; unrestricted research grants from NHMRC, Boehringer Ingelheim, CycloPharma, GlaxoSmithKline, Menarini, MundiPharma and philanthropic individuals and societies; non-financial support and other (research collaboration) from Restech, Italy during the conduct of the study. C. Thamrin has a patent WO 2006130922 A1 issued, which is broadly relevant to the work; and has intellectual property arrangements with Thorasys Medical Systems and Restech srl relating to research collaborations, but does not have any financial relationships with either company.

Support statement: This study was supported by a philanthropic grant from the Berg Family Foundation. Funding information for this article has been deposited with the Crossref Funder Registry.

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