Interactions between spirometry and oscillometry in patients with moderate to severe asthma

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To the Editor:

The small airways have previously been termed the "quiet zone" of the lungs, as airways ⩽2 mm in diameter are traditionally more difficult to assess and treat in asthma [1]. The small airways are of particular interest to clinicians due to the close association with type 2 inflammation and asthma control [2].

Spirometry involving a forced expiratory manoeuvre plays a pivotal role in the assessment of asthma, although current Global Initiative for Asthma (GINA) guidelines do not emphasise its role in measuring small airway dysfunction using forced expiratory flow rate between 25 and 75% of forced vital capacity ($FEF_{25–75}$). Moreover, impaired $FEF_{25–75}$ has been shown to be a sensitive marker of small airways disease in asthma [3]. Impaired $FEF_{25–75}$ is associated with airway hyperresponsiveness, greater rates of healthcare utilisation, higher fractional exhaled nitric oxide (F_{ENO}) and sputum eosinophils [4, 5].

Respiratory oscillometry involving effort-independent tidal breathing has conventionally been used in clinical research, paediatric medicine and for adult patients unable to generate the necessary expiratory flow rate required for spirometry testing [6]. Resistance heterogeneity measured between 5 and 20 Hz (R_5–R_{20}) reflects peripheral airway resistance and is highly concordant with small airway narrowing [7]. A recent large prospective study eloquently demonstrated the utility of oscillometry measurements reflecting small airway dysfunction across GINA asthma severities, including lung reactance measured either at 5 Hz (X_5) or as area under the reactance curve (A_X), as well as R_5–R_{20} [3].

A systematic review of physiological tests for detecting small airway dysfunction, including $FEF_{25–75}$ and oscillometry for the diagnosis of asthma, was inconclusive in determining the most useful modality [8]. Instead of an individual gold standard pulmonary function test, we postulate whether combining spirometry and oscillometry measurements of small airway function will be the way forward for optimal phenotyping of adult asthma patients. We aim to evaluate the interaction between spirometry- and oscillometry-defined small airway function using $FEF_{25–75}$ as a starting point. Therefore, we compared spirometry, oscillometry, type 2 biomarkers, severe exacerbations and asthma control between: 1) patients with impaired $FEF_{25–75}$ in conjunction with preserved or impaired oscillometry; and 2) patients with preserved $FEF_{25–75}$ in conjunction with preserved or impaired oscillometry; using cut offs of 60% for $FEF_{25–75}$ and 0.10 $kPa·L^{-1}·s^{-1}$ for R_5–R_{20} [9].

Data from 154 respiratory physician-diagnosed moderate-to-severe asthma patients were retrospectively collected from patients attending either the National Health Service specialist asthma clinic or during a screening visit for a prior clinical trial in the Scottish Centre for Respiratory Research. Notably, patients with other respiratory conditions, including COPD and bronchiectasis, were excluded from this study. Patients were divided into four groups based on the interaction between their spirometry and oscillometry small airway function: 1) preserved $FEF_{25–75}$ with preserved oscillometry: $FEF_{25–75}$ ⩾60%, R_5–R_{20} <0.10 $kPa·L^{-1}·s^{-1}$; 2) preserved $FEF_{25–75}$ with impaired oscillometry: $FEF_{25–75}$ ⩾ 60%, R_5–R_{20} ⩾0.10 $kPa·L^{-1}·s^{-1}$; 3) impaired $FEF_{25–75}$ with preserved oscillometry: $FEF_{25–75}$ <60%, R_5–R_{20} <0.10 $kPa·L^{-1}·s^{-1}$; and 4) impaired $FEF_{25–75}$ with impaired oscillometry: $FEF_{25–75}$ <60%, R_5–R_{20} ⩾0.10 $kPa·L^{-1}·s^{-1}$.

F_{ENO} was measured using NIOX VERO (Circassia, Oxford, UK) according to the manufacturer's instructions and American Thoracic Society (ATS) guidelines. Spirometry (Micromedical, Chatham, UK)

Shareable abstract (@ERSpublications)
Small airways dysfunction defined by spirometry and oscillometry together confers worse outcomes in moderate to severe asthma. This emphasises the importance of combining spirometry and oscillometry to characterise the small airway asthma phenotype. https://bit.ly/3CcaZ3e

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was performed according to European Respiratory Society (ERS)/ATS guidelines. Oscillometry was measured using IOS Masterscreen (Carefusion Hoechberg, Germany). Measurements were performed in triplicate to assess oscillometry according to the ERS technical standards, with oscillometry always performed prior to spirometry. Accuracy of resistance measurements was confirmed on each day with a 3 L calibration syringe (Masterscreen) and verified with the manufacturer's reference resistance device (0.2 kPa·L^{-1}·s^{-1}).

Blood testing was performed for peripheral blood eosinophils and total IgE. Asthma control was determined using the 6-point Asthma Control Questionnaire (ACQ), and the number of oral corticosteroid (OCS)-requiring asthma exacerbations in the preceding year was obtained from medical records.

Statistical analysis was performed using SPSS version 27. Data were assessed for outliers and for normality with Shapiro–Wilks prior to analysis. An overall analysis of variance was performed to evaluate

TABLE 1 Significant differences in spirometry, oscillometry, type 2 biomarkers, asthma control and OCS-requiring exacerbations comparing FEF_{25-75} ⩾60%, R_5–R_{20} <0.10 kPa·L^{-1}·s^{-1} *versus* FEF_{25-75} ⩾60%, R_5–R_{20} ⩾0.10 kPa·L^{-1}·s^{-1}; and FEF_{25-75} <60%, R_5–R_{20} <0.10 kPa·L^{-1}·s^{-1} *versus* FEF_{25-75} <60%, R_5–R_{20} ⩾0.10 kPa·L^{-1}·s^{-1}

	FEF_{25-75} ⩾60%		FEF_{25-75} <60%	
	R_5–R_{20} <0.1	R_5–R_{20} ⩾0.1	R_5–R_{20} <0.1	R_5–R_{20} ⩾0.1
FEV_1 (L)	3.24 (3.05–3.43) (n=40)	2.71 (2.48–2.95)** (n=22)	2.45 (2.20–2.69) (n=34)	1.91 (1.75–2.06)*** (n=58)
FEV_1 (%)	105.2 (100.5–109.9) (n=40)	97.0 (92.1–101.9)* (n=22)	79.6 (75.0–84.3) (n=34)	73.1 (68.1–78.2) (n=58)
FEF_{25-75} (L·s^{-1})	3.17 (2.88–3.46) (n=40)	2.62 (2.35–2.88)* (n=22)	1.35 (1.13–1.57) (n=34)	1.09 (0.97–1.21)$^{\#}$ (n=58)
FVC (L)	4.02 (3.77–4.26) (n=40)	3.37 (3.06–3.67)** (n=22)	3.90 (3.53–4.27) (n=34)	3.05 (2.81–3.29)*** (n=58)
FVC (%)	109.6 (104.7–114.5) (n=40)	101.6 (95.5–107.7) (n=22)	104.2 (99.1–109.4) (n=34)	96.2 (90.9–101.5) (n=58)
FEV_1/FVC	80.9 (79.2–82.6) (n=40)	80.8 (78.8–82.7) (n=22)	63.8 (60.4–67.3) (n=34)	63.8 (60.9–66.8) (n=58)
R_5 (kPa·L^{-1}·s^{-1})	0.38 (0.14) (n=40)	0.55 (0.18)*** (n=22)	0.39 (0.15) (n=34)	0.74 (0.36)*** (n=58)
R_{20} (kPa·L^{-1}·s^{-1})	0.34 (0.10) (n=37)	0.40 (0.16) (n=22)	0.35 (0.14) (n=34)	0.48 (0.21) *** (n=58)
R_5–R_{20} (kPa·L^{-1}·s^{-1})	0.06 (0.04) (n=37)	0.15 (0.07)*** (n=22)	0.05 (0.04) (n=34)	0.23 (0.24)*** (n=58)
X_5 (kPa·L^{-1}·s^{-1})	-0.10 (0.06) (n=30)	-0.17 (0.13)*** (n=17)	-0.12 (0.08) (n=31)	-0.30 (0.21)*** (n=44)
A_X (kPa·L^{-1})	0.28 (0.32) (n=39)	1.13 (0.83)*** (n=22)	0.44 (0.46) (n=33)	2.58 (3.77)*** (n=56)
f_{res} (Hz)	11.41 (3.89) (n=39)	18.48 (5.04)*** (n=22)	13.40 (5.63) (n=33)	24.23 (8.14)*** (n=56)
F_{ENO} (ppb)	15 (21) (n=33)	15 (19) (n=17)	29 (24) (n=28)	20 (17)* (n=42)
PBE (cells·µL^{-1})	225 (243) (n=38)	240 (314) (n=21)	350 (220) (n=29)	220 (328) (n=53)
Total IgE (kU·L^{-1})	64 (227) (n=35)	108 (306) (n=17)	105 (406) (n=25)	107 (370) (n=44)
ACQ	2.0 (1.5–2.5) (n=29)	2.2 (1.4–3.0) (n=21)	1.4 (1.0–1.9) (n=29)	2.4 (2.0–2.8)** (n=48)
OCS exacerbations	1 (2) (n=37)	1 (4) (n=17)	1 (4) (n=25)	4 (3)* (n=42)

Values presented as arithmetic means (95% confidence interval) except for oscillometry, type 2 biomarkers and oral corticosteroid (OCS)-requiring exacerbations, where median (interquartile range) is used. $^{\#}$: p=0.05, *: p<0.05, **: p<0.01, ***: p<0.001; denotes Bonferroni corrected comparisons between groups for either forced expiratory flow rate between 25 and 75% of forced vital capacity (FEF_{25-75}) ⩾60% or FEF_{25-75} <60%. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; R_5–R_{20}: resistance heterogeneity measured between 5 and 20 Hz; X_5: lung reactance measured at 5 Hz; A_x: area under the reactance curve; f_{res}: resonant frequency; F_{ENO}: fractional exhaled nitric oxide; PBE: peripheral blood eosinophils; ACQ: Asthma Control Questionnaire.

any significant differences in spirometry and ACQ (mean, 95% confidence interval) between the four groups, followed by pairwise comparisons (group 1 *versus* 2 and group 3 *versus* 4) with Bonferroni correction and a two tailed alpha error set at 0.05. Significant comparisons for oscillometry, type 2 biomarkers and OCS exacerbations (median, interquartile range) were performed using independent samples Kruskal–Wallis tests. A small amount of data for X_5, A_X and resonant frequency were unfortunately unavailable following interrogation of the oscillometry system. Additionally, to avoid over-investigation, not every patient had blood testing in cases where results were unlikely to change management. For missing data, analyses were performed with the number of data points stated in table 1. For National Health Service patients, Caldicott approval was obtained whilst for clinical trial patients informed consent and ethical approval was obtained *via* the East of Scotland research ethics service prior to data collection.

Mean overall demographic data were as follows: 102 subjects were female and 52 male; age 50 years; inhaled corticosteroid beclomethasone equivalent dose 1594 $\mu g \cdot day^{-1}$; ex-smokers 19%; body mass index 31 $kg \cdot m^{-2}$; forced expiratory volume in 1 s (FEV_1) 86%; long-acting β-agonist 82%; long-acting muscarinic antagonist 45%; leukotriene receptor antagonist 51%; theophylline 19%; oral antihistamines 47%; anti-IL5(rα) 21%; and anti-IL4rα 3%.

ACQ scores were significantly higher, indicating worse control in conjunction with more frequent exacerbations, in patients who exhibited combined impairment of $FEF_{25–75}$ and $R_5–R_{20}$, while there were no differences in peripheral blood eosinophils or total IgE (table 1). Patients with combined impairment of both $FEF_{25–75}$ and $R_5–R_{20}$ also had significantly lower FEV_1, $FEF_{25–75}$ and forced vital capacity, the latter indicating increased air trapping.

Pointedly, those with impaired spirometry as $FEF_{25–75}$ and impaired oscillometry as $R_5–R_{20}$ had significantly worse asthma control (as a 1.0-unit difference in ACQ) and more exacerbations requiring OCS than those with impaired $FEF_{25–75}$ but preserved $R_5–R_{20}$. The presence of impaired peripheral flow and resistance was not, however, associated with altered peripheral blood eosinophils or total IgE. The absolute difference in ACQ score was 1.0, which exceeded the minimal clinically important difference of 0.5 units. Previously it has been shown that each 1.0-point increase in ACQ score is associated with a 50% increased exacerbation risk in moderate to severe asthmatics [10]. In other words, the results with regards to ACQ and exacerbations point to the findings being clinically meaningful. Indeed, a previous health informatics study in mild-to-moderate asthma patients showed that combined impairment of spirometry and oscillometry, as $FEF_{25–75}$ and $R_5–R_{20}$, respectively, showed significantly worse asthma control defined by increased OCS and short-acting β-agonist use over 2 years [11].

Biological variability, a measurement of natural fluctuation over time, can be used as a surrogate for the minimal change that must be exceeded for a clinically significant treatment effect to occur [12]. The absolute differences in FEV_1 and $FEF_{25–75}$ were 540 mL and 260 $mL \cdot s^{-1}$, respectively, between groups with impaired $FEF_{25–75}$ with or without impaired $R_5–R_{20}$, which exceeded the biological variability values in severe asthma, amounting to 150 mL for FEV_1 and 210 $mL \cdot s^{-1}$ for $FEF_{25–75}$ (table 1) [12].

In the present study, our overall cohort of uncontrolled moderate-to-severe asthma patients had a well preserved mean FEV_1 of 86%, but impaired small airway function, as evidenced by $FEF_{25–75}$ of 54% and R_5 of 169%. We appreciate the limitation of our study due to its retrospective nature, but we believe that these data emphasise the important synergistic effect of combining spirometry and oscillometry measurements as useful tools in identifying those with clinically relevant small airway dysfunction. Perhaps these results will lead current guidelines to adopt more widespread use of oscillometry as an important adjunct and the incorporation of small airway dysfunction as an additional treatable trait in the management of asthma in the near future.

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