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Combining low-frequency oscillometry and spirometry measurements in relation to asthma control and exacerbations in moderate-to-severe asthma

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Clinical Implications

Patients with combined impairment of reactance at 5 Hz (X5) and forced expiratory volume in 1 second have significantly worse asthma control and more frequent severe exacerbations.

Respiratory oscillometry is an effort-independent pulmonary function test that can assess respiratory impedance over a range of frequencies, comprising resistance (R) and reactance (X) moieties. Governed by Poiseuille's law, airway resistance is largely determined by airway caliber and length, whereas reactance comprises elastance and inertance components and can be used as a measurement for lung stiffness at various frequencies. Low-frequency sound waves penetrate further down the airways and hence reflect changes in the whole lung. Therefore, total airway resistance can be assessed by measuring at 5 Hz (R5), whereas airway compliance can be assessed as reactance at 5 Hz (X5).[1] Recently it has been shown that adults with a positive bronchodilator response assessed by R5 or X5 have a higher prevalence of asthma and wheezing.[2] Furthermore, X5 has greater sensitivity in identifying poor asthma control than spirometry.[3] Nonetheless, spirometry measurement of forced expiratory volume in 1 second (FEV_1) still remains the main investigation of choice in current global asthma guidelines.[4]

Combining oscillometry and spirometry measurements together may be useful in identifying poor asthma control defined by increased use of oral corticosteroids (OCS) and short-acting β-agonists in relation to small airways function as resistance heterogeneity between 5 and 20 Hz (R5-R20) and forced expiratory flow rate between 25% and 75% of forced vital capacity (FEF_{25-75}%).[5] Although R5-R20 correlates with FEF_{25-75}, the current significance of FEF_{25-75} is still somewhat debated.

In the study, we evaluate asthma control as the Asthma Control Questionnaire (ACQ), OCS-requiring severe exacerbations, and type 2 (T2) biomarkers (peripheral blood eosinophils, fractional exhaled nitric oxide, and total and specific IgE) in adult moderate-to-severe asthma patients with impaired oscillometry with or without impaired spirometry.

Data from 94 respiratory physician-diagnosed moderate-to-severe asthma patients were retrospectively collected from outpatients attending our unit during normal clinical evaluation. Patients were divided into 2 groups based on the interplay between oscillometry and spirometry measurements: (a) impaired X5 (or R5) with impaired FEV_1 and (b) impaired X5 (or R5) with preserved FEV_1. Values of −0.20 kPa/L/s for X5, 0.50 kPa/L/s for R5, and 80% for FEV_1 were chosen to define impairment.

Fractional exhaled nitric oxide (FeNO) was measured using NIOX VERO (Circassia, Oxford, UK) according to the manufacturer's instructions and American Thoracic Society (ATS) guidelines. Spirometry (Micro Medical, Chatham, UK) was performed according to European Respiratory Society (ERS)/ATS guidelines. Oscillometry was measured using either IOS Masterscreen (Carefusion, Hoechberg, Germany) or TremoFlo (Thorasys, Montreal, QC, Canada). Measurements were performed in triplicate to assess oscillometry according to the ERS technical standards with oscillometry always performed before spirometry. Blood testing was performed for peripheral blood eosinophils, total IgE (kU/L), and number of positive specific IgE antibodies (fluorescence enzyme linked immunoassay [Phadia Immunocap 250]) to defined common allergens including house dust mite, grass, cat, dog, and silver birch. In patients taking biologics, data on T2 biomarkers (peripheral blood eosinophils, FeNO, and total and specific IgE) preceded treatment initiation to avoid potential confounding. Asthma control was determined using the 6-point ACQ. The number of OCS-requiring asthma exacerbations in the preceding year was noted, determined by an oral prednisolone dose of 40 mg daily for at least 5 consecutive days.

Statistical analysis was performed using SPSS version 27 (Portsmouth, UK). Data were initially assessed for outliers and normality before analysis. Independent Student's *t* tests were performed to evaluate any significant differences in ACQ, OCS-requiring exacerbations, T2 biomarkers, and pulmonary function between the 2 groups using a 2-tailed alpha error set at 0.05. Data for R5-R20 were logarithmically transformed to normalize its distribution before analysis. Values provided in this paper are all arithmetic means (95% confidence interval [CI]) except for R5-R20 where geometric mean (95% CI) was used. Caldicott approval was obtained for National Health Service patients, whereas for clinical trial patients, ethical approval was obtained via the East of Scotland research ethics service before data collection.

The mean overall demographic data were as follows: gender (F/M) 72/22; age 52; body mass index 32.7 kg/m^2; inhaled corticosteroid beclomethasone dipropionate equivalent dose 1694 μg; percentage of patients taking long-acting β-agonist 78%; long-acting muscarinic-antagonist 53%; leukotriene receptor antagonist 59%; theophylline 22%; oral antihistamines 54%; anti-IL5(rα) 18%; anti-IL4rα 4%; FEV_1 76%; FEF_{25-75} 41%; and R5 209%.

Table I and Table E1 (available in this article's Online Repository at www.jaci-inpractice.org) present significant differences in ACQ, OCS-requiring exacerbations, T2 biomarkers, and pulmonary function in patients with impaired oscillometry (R5 or X5) with or without impaired spirometry (FEV_1). Patients with combined impairment of X5 and FEV_1 had significantly worse ACQ, OCS-requiring exacerbations, R5-R20, and AX than those with impaired X5 but preserved FEV_1 (Figure 1). A similar pattern was seen for patients with combined impairment of R5 and FEV_1, aside from OCS-requiring exacerbations that were borderline significant ($P = .05$) (Figure 1). FeNO was significantly worse in patients with combined impairment of R5 and FEV_1, but no differences were observed for other T2 biomarkers.

TABLE I. Significant comparisons in Asthma Control Questionnaire (ACQ), oral corticosteroid (OCS) exacerbations, and type 2 biomarkers in patients with impaired oscillometry with or without impaired spirometry

	R5 ≥ 0.5 kPa/L/s		X5 ≤ −0.2 kPa/L/s	
Clinical outcomes	**FEV_1 ≥ 80%**	**FEV_1 < 80%**	**FEV_1 ≥ 80%**	**FEV_1 < 80%**
ACQ	2.2 (1.8-2.7) (n = 42)	2.9 (2.5-3.3)* (n = 44)	2.2 (1.8-2.7) (n = 25)	2.9 (2.5-3.3)* (n = 35)
OCS exacerbations	2.3 (1.5-3.1) (n = 31)	3.3 (2.6-4.0)* (n = 39)	1.8 (0.7-2.9) (n = 18)	3.2 (2.5-4.0)* (n = 30)
FeNO (ppb)	24 (17-32) (n = 36)	36 (27-44)* (n = 38)	27 (17-37) (n = 25)	35 (26-43) (n = 32)
PBE (cells/μL)	329 (258-400) (n = 42)	324 (247-401) (n = 44)	308 (241-374) (n = 25)	289 (203-376) (n = 34)
No. of positive specific IgE	1.4 (0.8-2.0) (n = 33)	1.7 (1.1-2.3) (n = 33)	1.1 (0.5-1.7) (n = 20)	1.3 (0.7-1.9) (n = 27)
Total IgE (kU/L)	338 (183-494) (n = 34)	296 (206-387) (n = 40)	248 (139-357) (n = 20)	262 (171-354) (n = 29)

Values presented as arithmetic means (95% CI) except for R5-R20 where geometric means (95% CI) were used. Specific IgE are shown as the mean number of positive responses ≥0.35 kUA/L.

CI, Confidence interval; *FeNO*; fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second.

*$P = .05$, $P < .05$, denotes significant comparisons between groups for either $FEV_1 \geq 80\%$ or $FEV_1 < 80\%$.

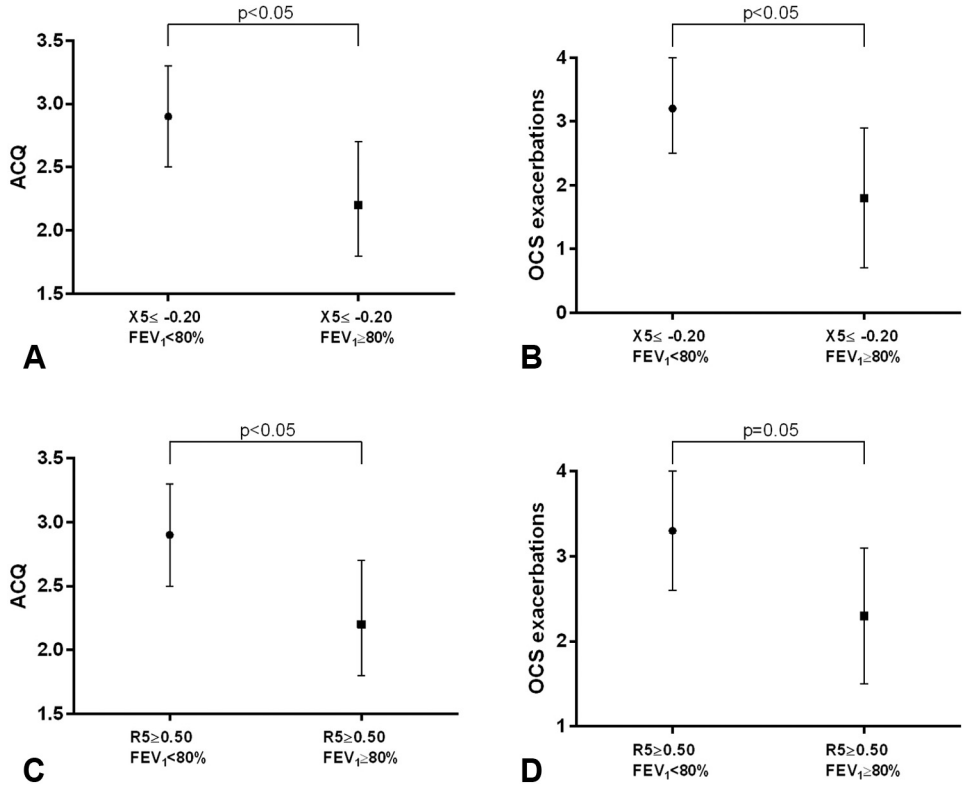

FIGURE 1. Comparisons in Asthma Control Questionnaire (ACQ) and exacerbations in patients with combined impairment of oscillometry and spirometry versus those with impaired oscillometry but preserved spirometry, presented as means and 95% confidence interval. *FEV_1*, Forced expiratory volume in 1 second; *OCS*, oral corticosteroids.

Our results show that patients with combined impairment of X5 and FEV_1 had a 78% higher exacerbation risk and a mean 0.7-unit higher ACQ score than those with impaired X5 but preserved FEV_1 (Table I), in keeping with clinically relevant differences in disease control. On the contrary, T2 biomarkers including FeNO, peripheral blood eosinophils, and specific and total IgE were not significantly different when comparing patients with impaired X5 with or without impaired FEV_1. The only notable exception was FeNO in the impaired R5 with or without FEV_1 impairment analysis, but this did not exceed the biological variability value of 15 for severe asthma.[6]

Moreover, patients with combined impairment of X5 and FEV_1 had significantly worse indicators of small airways disease expressed as either R5-R20 or AX than those with impaired X5 but preserved FEV_1. The observed differences of 0.12 kPa/L/s for R5-R20 and 2.63 kPa/L for AX greatly exceeded previously reported biological variability values of 0.04 kPa/L/s and 0.39 kPa/L, respectively, inferring that these differences are likely to be clinically relevant.[6] In turn, small airways dysfunction is associated with poor asthma control in asthma.[7]

There are limitations associated with these data including its retrospective nature. Furthermore, we appreciate that in real-life clinical practice, most clinicians would use spirometry rather

than oscillometry as a starting point. We chose pragmatic cutoff values for oscillometry and spirometry that we routinely employ in our service clinic to denote clinically abnormal values. Our findings highlight the potential advantage of combining both spirometry and oscillometry measurements in fully characterizing airflow limitation in moderate-to-severe asthma.

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Conflicts of interest: B. J. Lipworth reports nonfinancial support (equipment) from GSK; equipment, consulting, and talks from Thorasys; consulting, advisory board, and talks from Circassia; grants, personal fees (consulting, talks, and advisory board), and other support (attending ATS and ERS) from AstraZeneca; grants, personal fees (consulting, talks, and advisory board), and other support (attending ERS) from Teva; grants, personal fees (consulting talks and advisory board), and other support from Chiesi; grants and personal fees (consulting, advisory board, and talks) from Sanofi; personal fees (consulting, talks, and advisory board) from Circassia, in relation to the submitted work; personal fees (consulting) from Lupin, personal fees (consulting and talks) from Glenmark, personal fees (consulting) from Vectura, personal fees (consulting) from Dr Reddy, personal fees (consulting) from Sandoz; grants, personal fees (consulting, talks, and advisory board), and other support (attending BTS) from Boehringer Ingelheim; grants and personal fees (advisory board and talks) from Mylan outside of the submitted work; and the son of B. J. Lipworth is presently an employee of AstraZeneca. R. Chan declares that he has no relevant conflicts of interest.

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TABLE E1. Significant comparisons in pulmonary function in patients with impaired oscillometry with or without impaired spirometry

	R5 ≥ 0.5 kPa/L/s		X5 ≤ −0.2 kPa/L/s	
	FEV_1 ≥ 80%	FEV_1 < 80%	FEV_1 ≥ 80%	FEV_1 < 80%
FEV_1 (L)	2.45 (2.31-2.59) (n = 44)	1.62 (1.47-1.77)*** (n = 50)	2.29 (2.10-2.47) (n = 26)	1.54 (1.37-1.71)*** (n = 38)
FEF_{25-75} (L/s)	1.92 (1.70-2.13) (n = 44)	0.90 (0.75-1.05)*** (n = 50)	1.73 (1.44-2.02) (n = 26)	0.84 (0.69-0.99)*** (n = 38)
FVC (L)	3.31 (3.11-3.51) (n = 44)	2.79 (2.55-3.04)** (n = 50)	3.10 (2.88-3.33) (n = 26)	2.70 (2.42-2.98)* (n = 38)
FEV_1/FVC	74.0 (71.6-76.3) (n = 44)	59.9 (55.9-63.9)** (n = 50)	72.8 (69.8-75.8) (n = 26)	59.5 (54.7-64.2)*** (n = 38)
R5 (kPa/L/s)	0.68 (0.63-0.73) (n = 44)	0.80 (0.72-0.88)* (n = 50)	0.71 (0.63-0.79) (n = 26)	0.83 (0.73-0.93) (n = 38)
R20 (kPa/L/s)	0.49 (0.46-0.52) (n = 43)	0.48 (0.44-0.52) (n = 49)	0.50 (0.44-0.55) (n = 26)	0.48 (0.43-0.53) (n = 38)
R5-R20 (kPa/L/s)	0.15 (0.12-0.18) (n = 44)	0.26 (0.22-0.32)*** (n = 50)	0.18 (0.13-0.23) (n = 26)	0.30 (0.26-0.36)*** (n = 38)
X5 (kPa/L/s)	−0.24 (−0.28 to −0.21) (n = 37)	−0.42 (−0.49 to −0.35)*** (n = 42)	−0.29 (−0.32 to −0.25) (n = 26)	−0.45 (−0.52 to −0.38)*** (n = 38)
AX (kPa/L)	1.90 (1.46-2.34) (n = 43)	4.56 (3.61-5.50)*** (n = 48)	2.50 (1.90-3.11) (n = 26)	5.13 (4.06-6.20)*** (n = 38)
F_{res} (Hz)	20.77 (18.73-22.81) (n = 41)	26.20 (24.41-27.98) (n = 44)	23.28 (20.63-25.94) (n = 24)	27.68 (25.89-29.47)** (n = 34)

FEF_{25-75}, forced expiratory flow rate between 25% and 75% of forced vital capacity (FEF_{25-75}%); *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity. *$P < .05$; **$P < .01$; and ***$P < .001$.