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Title: Airwave oscillometry and patient reported outcomes in persistent asthma**Authors:** Dr Chris RuiWen Kuo MBChB, Dr Brian Lipworth MD**Affiliation:** Scottish Centre for Respiratory Research
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b.j.lipworth@dundee.ac.uk**Conflicts of interest**

Dr. Kuo reports personal fees from Circassia, AstraZeneca and Chiesi outside the submitted work.

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Abbreviations/ Acronyms:

ACQ-6	Asthma control questionnaire 6
AOS	Airwave oscillometry
AX	Area under the reactance curve
BDP	Beclomethasone dipropionate
CI	Confidence interval
FeNO	Fractional exhaled nitric oxide
FEV ₁	Forced expiratory volume in 1 second
FEF ₂₅₋₇₅	Forced expiratory flow at 25-75% of pulmonary volume
FOT	Forced oscillation technique
ICS	Inhaled corticosteroids
IOS	Impulse oscillometry
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
mAQLQ	Mini asthma quality of life questionnaire
PRO	Patient reported outcomes
R5	Resistance at 5 Hz
R5-R19	Difference between resistance at 5 Hz and 19 Hz
R5-R20	Difference between resistance at 5 Hz and 20 Hz
SAD	Small airway dysfunction
T2	Type 2 airway inflammation

Airwave oscillometry (AOS: Tremoflo, Thorasys, Montreal) is a modern forced oscillation technique (FOT) using a vibrating mesh to superimpose forced oscillations of sound waves on top of normal tidal breathing to measure respiratory impedance as lung resistance (R) and reactance (X), whereas the older impulse oscillometry (IOS: Jaeger Masterscreen, Carefusion Hoechberg, Germany) uses a loudspeaker source. AOS measurements strongly correlate with IOS^{1,2} and quantify the degree of small airways dysfunction (SAD) as either peripheral airway resistance in terms of heterogeneity (AOS: R5-R19; IOS: R5-R20) or peripheral reactance (i.e. compliance) as area under the reactance curve (AX).

In asthmatics with a preserved forced expiratory volume in 1 second (FEV_1), the presence of SAD as measured with an increase in R5-R20 was associated with significantly higher long term oral corticosteroid and inhaled salbutamol use.³ In more severe, poorly controlled asthma patients, IOS measurements of R5-R20 and AX, but not spirometry (FEV_1), were more closely related to disease activity as measured by asthma control questionnaire (ACQ-6).⁴ The fractional exhaled breath nitric oxide (FeNO) is a non-invasive surrogate for type 2 (T2) airway inflammation which relates to airway hyper-responsiveness. SAD asthma phenotype is an individual with normal FEV_1 and increased R5-R20. We have reported that the SAD phenotype is related to an increased blood eosinophil count.⁵

We therefore investigated the relationship of AOS to patient reported outcomes (PRO) of asthma control, namely ACQ-6 and mini asthma quality of life questionnaire (mAQLQ). In particular, we were interested in ACQ-6 which is a strong predictor of future exacerbation risk.^{6,7}

Retrospectively, we evaluated a cohort of 46 adult patients with persistent asthma who voluntarily attended our centre for clinical trial screening into clinical trials. This was a completely different cohort to that previously reported using IOS.⁵ AOS and spirometry (Micromedical, Chatham, United Kingdom) were performed in triplicate according to European Respiratory Society guidelines and spirometry was always done after the AOS measurements. Consents were obtained from all patients for their screening data to

be accessed. Comparisons of ACQ-6, AOS and pre-bronchodilator spirometry were analysed with each predefined cut point value: R5-R19 (kPa/L/s) <0.08 vs ≥ 0.08 ⁸, AX (kPa/L) <1.0 vs ≥ 1.0 ; FEV₁ (% predicted) <80 vs ≥ 80 ; FEF₂₅₋₇₅ (% predicted) <50 vs ≥ 50 . Differences in percent reversibility of AOS and spirometry following inhaled salbutamol 400µg were compared between well and poorly controlled asthma defined by ACQ-6 of <0.75 and ≥ 1.5 respectively. FeNO data were log-transformed to normalise the distribution. Unpaired Student's *t* tests was used to compare each outcome with alpha error set at 0.05 (2-tailed).

The overall mean age was 51 years, FEV₁ 87% predicted, R5 142%, inhaled corticosteroid (ICS) beclometasone dipropionate (BDP) equivalent of 620µg, 65 % were taking long-acting beta agonist (LABA), 11% long-acting muscarinic antagonist (LAMA) and 37% leukotriene receptor antagonist (LTRA). Using a cut point for R5-R19 of 0.08 kPa/L/s, there were differences in mean ACQ-6 values: 1.01 vs 2.07 (95% CI for difference -1.66, -0.45; $p<0.01$) (Fig 1) and in mAQLQ (symptoms): 5.23 vs 4.30 (CI 0.10, 1.74; $p<0.05$). For AX with a cut point of 1.0 kPa/L there were differences in ACQ-6: 0.99 vs 1.93 (CI -1.55, -0.33; $p<0.01$), in mAQLQ symptoms: 5.28 vs 4.42 (CI 0.06, 1.66; $p<0.05$) and mAQLQ activity: 5.92 vs 5.01 (CI 0.004, 1.81; $p<0.05$). For the R5-R19 there was also a difference in geometric mean FeNO (ppb): 30 vs 45 (CI 25 - 38%; $p<0.05$).

For FEV₁ cut point of 80% predicted, differences were seen in ACQ-6: 2.20 vs 1.27 (CI 0.11, 1.76; $p<0.05$) and mAQLQ symptoms: 4.05 vs 5.09 (CI -1.93, -0.16; $p<0.05$) but not FeNO. For FEF₂₅₋₇₅ cut point of 50% predicted there were differences in ACQ-6 1.90 vs 1.23 (CI 0.003, 1.34; $p<0.05$) and geometric mean of FeNO 47 vs 30 ppb (CI 29 – 170%; $p<0.05$).

In a subgroup of 30 asthmatic patients with preserved FEV₁ $\geq 80\%$, using ACQ-6 cut point of <1 vs ≥ 1 defining poor asthma control, there were significant differences in AOS measurements for R5: 0.37 vs 0.46 kPa/L/s (CI 0.01, 0.18; $p<0.05$), R5-R19: 0.05 vs 0.12 kPa/L/s (CI 0.01, 0.14; $p<0.05$) and AX: 0.88 vs 2.06 kPa/L (CI 0.04, 2.32; $p<0.05$).

For ACQ-6 using a cut point of <0.75 vs ≥ 0.75 , there were differences in mean percent reversibility for R5: 11 vs 24% (CI -22, -5; $p<0.01$) and R5-19: 18 vs 51% (CI -60, -6; $p<0.05$), but not for FEV₁ ($p=0.05$). For ACQ-6 at a cut point of <1.5 vs ≥ 1.5 , differences were observed in percent reversibility for R5: 15 vs 25% (CI -18, -2; $p<0.05$), R5-19: 27 vs 55% (CI -53, -3; $p<0.05$) and FEV₁: 5 vs 10% (CI -7, -1; $p<0.05$).

Our results show asthmatic patients with SAD defined by R5-R19 or AX have significantly poorer asthma control and quality of life in terms of symptoms. Our findings are similar to those of Foy et al⁸ who also reported good correlations between R5-R20 (IOS) and asthma control using patient based computational modelling. However, another study concluded that IOS has no discriminative capacity to classify patients according to the degree of asthma control.⁹ In the present study, we used a lower cut off for AX of 1.0 kPa/L using AOS as compared to 1.5 kPa/L using IOS in a previous study.⁵ The reason for this is that AOS is more sensitive than IOS in detecting altered lung compliance.²

We observed that the degree of bronchodilator reversibility was relatively greater with AOS than spirometry. Notably, for an ACQ-6 cut point of 0.75 there was a statistically significant difference in ACQ-6 for R5 and R5-R19 but not FEV₁. This finding is consistent with a previous study comparing reversibility of IOS and spirometry in asthma in terms of relative bronchodilation and bronchoconstriction. Hence, AOS may be more sensitive for detecting reversibility in patients with a preserved FEV₁ where there is little room for improvement.¹⁰

The main limitation of our study is that the data were retrospective and cross-sectional. A prospective serial evaluation might be able to better correlate AOS with PRO. We utilised FeNO as a surrogate measure of type 2 airway inflammation but did not measure sputum eosinophils. It would be helpful to perform a prospective evaluation of the utility of AOS to predict exacerbations although this has already been documented retrospectively by Manoharan et al³ over two years.

In conclusion, peripheral lung resistance and reactance measured by AOS are related to patient reported outcomes of asthma control and quality of life. AOS was also more sensitive at detecting bronchodilator reversibility in relation to asthma control. We propose that measuring AOS should complement spirometry as part of the routine work up of asthma patients in a real life clinic setting.

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Figure legend

Figure 1

ACQ values are shown as means and SEM for significant comparisons according to R5-R19, AX, FEV₁ % predicted and FEF₂₅₋₇₅ % predicted.

Figure 1

