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Abstract: Outcomes measured with impulse oscillometry are more closely related to asthma control than spirometry in moderate to severe asthma.

1 **Utility of impulse oscillometry in patients with moderate to severe**
2 **persistent asthma**

3

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17 **Capsule Summary:** Outcomes measured with impulse oscillometry are more
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19 asthma.

20 **Key Words:** Impulse oscillometry, asthma, control

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22 **Word Count** =1056

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25 To the Editor:

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27 We have previously shown in a cohort of asthmatic patients that impulse
28 oscillometry (IOS) and spirometry are equally useful in predicting asthma
29 control as assessed by prescriptions of oral corticosteroid and inhaled
30 albuterol using health informatics¹. These were patients referred from primary
31 care for screening into clinical trials. We wanted to know how IOS and
32 spirometry were related to the asthma control questionnaire (ACQ) in a real
33 life secondary care clinic setting. In particular we were interested to see if IOS
34 outcomes reflecting frequency dependent heterogeneity², namely the
35 difference in resistance at 5Hz and 20Hz (R5-R20) and the reactance area
36 (AX) between 5Hz and the resonant frequency (RF), are more closely
37 associated with worse asthma control, as has previously been described in
38 children with asthma³.

39 We have evaluated a separate series of 108 unselected patients attending a
40 National Health Service (NHS) asthma secondary care clinic, who completed
41 an ACQ-5 score⁸ in addition to having spirometry and IOS, as part of their
42 usual care. Their current asthma therapy at the time of the clinic visit was also
43 documented. We routinely perform IOS, spirometry and ACQ in our clinic,
44 hence this audit of usual clinical care did not require ethics approval, although
45 Caldicott guardian approval was obtained in order to allow appropriate access
46 to the patient identifiable NHS data. IOS (Jaeger Masterscreen, Hochberg
47 Germany) and spirometry (Micromedical Chatham Kent, UK) were performed
48 in triplicate according to European Respiratory Society guidelines.

49 We analysed the IOS and spirometry data according to both ACQ-5 and
50 current salbutamol use comparing predefined cut-off values for each
51 measurement as follows: FEV₁ <80 % versus ≥80 % predicted; FEF₂₅₋₇₅ <50
52 % versus ≥50% predicted; FEV₁/FVC ratio <0.70 versus ≥0.70; R5 < 150 %
53 versus ≥150 % predicted; R20 <150% versus ≥150% predicted, R5–R20 < 0.1
54 versus ≥0.1 kPa/l.s (i.e. 1 cmH₂O/l.s); AX <0.8 versus ≥ 0.8 kPa/l (i.e. 8
55 cmH₂O/l), RF (resonant frequency) <15 versus ≥ 15Hz. Comparisons for each
56 outcome were made by unpaired Students t tests with alpha error set at 0.05
57 (two tailed).

58 The patients (n=108) had an overall mean age of 42 years, FEV₁ of 81%
59 predicted, FEV₁/FVC of 0.68, R5 of 178 % predicted, R5-R20 of 0.16 kPa/l.s
60 and ACQ-5 score of 2.37. All patients were receiving inhaled corticosteroids
61 (ICS) in a median beclomethasone equivalent dose of 800 µg/day, 80% were
62 taking long acting beta-agonists (LABA) and 36% were taking leukotriene
63 receptor antagonists.

64 The results showed that IOS measurements of R5-R20, AX and RF, but none
65 of the spirometry measurements were significantly different in terms of worse
66 control as ACQ-5 (Table and Figure), while only R5-R20 was significantly
67 different for increased salbutamol use: 5 vs 8 puffs /day (P=0.006).
68 Furthermore when the data were analyzed using lower cut-off values for
69 FEV₁/FVC ratio (<0.6 and <0.5) and FEF₂₅₋₇₅ (<40% and <30% predicted)
70 there were also no significant differences in ACQ-5 .

71 Our data would therefore suggest that in a real life clinic setting IOS rather
72 than spirometry is more closely related to asthma control based on the ACQ-5
73 score. Overall our patients had moderate to severe persistent asthma in

74 keeping with a high total airway resistance (R5) of 178% and mean ACQ
75 score of 2.37⁴. Indeed the lower bound of the 95%CI for ACQ was higher than
76 the cut off value of 1.5 for poorly controlled asthma for variables, even in
77 those patients with a preserved FEV₁ ≥ 80% (Figure). Pointedly the ACQ
78 score has been shown to be a highly predictive proxy for the future risk of
79 asthma exacerbations⁵.

80 The R5-R20 and AX are indicative of frequency dependent heterogeneity for
81 respiratory resistance and reactance respectively throughout the lung ². We
82 were not able to measure resistance or reactance at frequencies <5Hz which
83 might better reflect smaller airways . Our patients had evidence of large
84 airway obstruction as reflected by a mean FEV₁/FVC ratio of 0.68 and a mean
85 FEV₁ of 81% predicted . As such our data would suggest that IOS is a more
86 sensitive index of airway obstruction than spirometry irrespective of the site of
87 obstruction at least in patients with mild to moderate persistent asthma .
88 Nonetheless we observed that neither R5 (reflecting total airway resistance)
89 nor R20 (reflecting central airway resistance) were associated with a
90 significant difference in ACQ, in contrast to the significant difference seen with
91 R5-R20 . Our data are similar to those of Shi et al. where the heterogeneity of
92 resistance (R5-20) or reactance (AX) were more predictive of asthma control
93 than either R5 or X5 in asthmatic children³ . However in a cohort of patients
94 with no evidence of large airway obstruction who had a preserved FEV₁>80%
95 ,an abnormal R5-R20 was associated with increased use of oral corticosteroid
96 and albuterol ⁶.

97 We did not however observe a significant difference with ACQ in relation to
98 FEF₂₅₋₇₅ which is a rather variable volume dependent measurement of flow

99 rate ⁷. Indeed even when using a lower cut off value <30 % predicted for
100 FEF₂₅₋₇₅ there was still no significant difference in ACQ score. IOS is
101 considered to be more physiological than spirometry as it is performed during
102 normal quiet breathing and therefore not affected by forced expiratory
103 changes which occur during spirometry². The present data differ from our
104 previous observations¹ where we found that IOS and spirometry measures
105 were equally useful as markers of asthma control using prescribing data for
106 oral corticosteroid and inhaled albuterol use. This may be explained by the
107 patients actually recording their ACQ score in the clinic at the same time as
108 having their pulmonary function performed, perhaps resulting in a greater
109 degree of concordance between physiology and symptoms. We elected to
110 use the abbreviated ACQ-5 score because we did not want to confound the
111 results by including FEV₁% or albuterol use. Moreover it has been shown that
112 the abbreviated ACQ-5 score is as sensitive as the ACQ-7 score⁸.

113 In conclusion impulse oscillometry outcomes reflecting frequency dependent
114 heterogeneity appear to be more closely related to asthma control than
115 spirometry in patients with moderate to severe persistent asthma . Further
116 prospective trials are indicated to assess whether serial long term IOS
117 measurements may help guide decision making for patients with persistent
118 asthma with disproportionate small airways disease, especially since health
119 economics studies have suggested that using extra fine particle inhalers
120 containing ICS inhalers may confer better long term outcomes⁹.

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Figure 1.

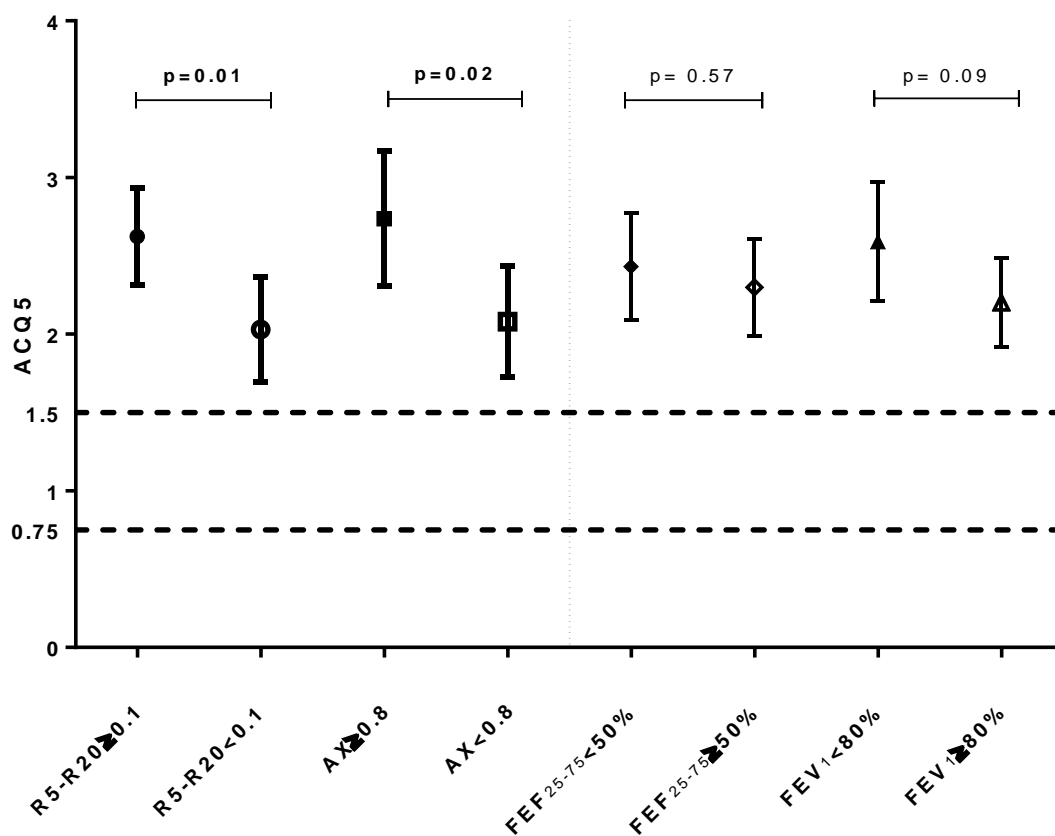


Figure Legend

Mean and 95% CI for ACQ5 score when stratified for both IOS and spirometry cut off values .Interrupted lines denote cut off values for ACQ score for well controlled (<0.75) and poorly controlled asthma (≥1.50).Values for R5-R20 are kPa/l.s and AX are kPa/l , FEV₁ and FEF₂₅₋₇₅ are % predicted

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Table 1. Pulmonary function measures in relation to ACQ5 score

	ACQ5	n	ACQ5	n	p value
Impulse oscillometry					
R5-R20 (kPa/L.s)	<0.1		≥0.1		0.01
	2.03 (0.17)	46	2.62 (0.15)	62	
R5 (% pred)	<150%		≥150%		0.18
	2.18 (0.17)	42	2.49 (0.15)	66	
R20 (% pred)	<150%		≥150%		0.30
	2.50 (0.15)	51	2.26 (0.17)	57	
AX (kPa/L)	<0.8		≥0.8		0.02
	2.08 (0.17)	38	2.74 (0.21)	41	
RF (Hz)	<15		≥15		0.04
	2.06 (0.20)	31	2.65 (0.19)	48	
Spirometry					
FEV₁ (% pred)	<80%		≥80%		0.09
	2.59 (0.19)	47	2.20 (0.14)	61	
FEV₁/FVC (Ratio)	<0.7		≥0.7		0.49
	2.29 (0.17)	55	2.45 (0.16)	53	
FEF₂₅₋₇₅ (% pred)	<50%		≥50%		0.57
	2.43 (0.17)	59	2.30 (0.15)	49	

Data for AX and RF were only available in a subgroup of n=79 patients, while all other variables were on the full dataset of n=108. Values for ACQ-5 are means (SEM).