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Title: Small Airways Dysfunction is Associated with Poorer Asthma Control

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Take home message

In asthmatics with a preserved FEV_1, small airways dysfunction defined by FEF_{25-75} and R5-R20 was associated with poorer long-term control.

Small Airways Dysfunction is Associated with Poorer Asthma Control

The clinical relevance of the small airways in persistent asthma has been gaining greater recognition in recent years [1]. Studies have shown that a significant proportion of asthmatics on standard treatment fail to achieve satisfactory asthma control. For example, in one study of 3421 asthmatic subjects who underwent guideline driven dose titration with standard inhaled corticosteroids (ICS) / long-acting beta-agonist (LABA) combination therapy over 1 year, only 41% achieved total control of their asthma while 71% were well controlled [2]. Anderson et al [3] found a high prevalence of adult patients with persistent small airway dysfunction determined by impulse oscillometry (IOS, as R5-R20) and spirometry (as FEF_{25-75}) across British Thoracic Society (BTS) treatment steps for asthma, many of whom had a preserved FEV_1. This in turn suggests an unmet clinical need in terms of patients who may have a small airway asthma phenotype.

We therefore evaluated whether small airways dysfunction was associated with worse control in adult asthmatics with a preserved FEV_1 (FEV_1 > 80% predicted). Spirometry and IOS measurements from unselected asthmatics referred from primary care who attended for screening visits for clinical trials were linked to prescription data. The prescription data were obtained from the Tayside Health Informatics Centre which links all community dispensed prescriptions using a person's unique identifier, the Community Health Index. Spirometry and IOS measurements from asthmatics were linked to oral corticosteroid and short-acting beta-agonist (SABA) use. We evaluated if small airways dysfunction, defined as FEF_{25-75} < 70%, or peripheral airway resistance as R5-R20 > 0.07 $kPa \cdot L^{-1} \cdot s$ was associated with increased oral corticosteroid and SABA use. Oral steroid and SABA use 1 year prior and 1 year following the index measurements were determined i.e. whether or not patients had an oral steroid prescription for an asthma exacerbation or the use of > 4 or ≤ 4 SABA inhalers.

Research ethics committee approval was obtained for all the studies the patients were being screened into and Caldicott Guardian approval was obtained to transfer the data to the Health Informatics Centre. IOS (Jaeger Masterscreen IOS, Hochberg, Germany) was performed in triplicate in accordance with manufacturer's guidelines. A SuperSpiro spirometer (Micro Medical Ltd., Chatham, Kent, United Kingdom) was used in triplicate in accordance with European Society guidelines [4]. Logistic regression analysis was applied to calculate the odds ratios (OR) for steroid and salbutamol use in the different groups. Age, gender, ICS, LABA and leukotriene receptor antagonists (LTRA) use were all included as covariates to calculate the adjusted OR and 95% confidence interval.

302 out of 442 (68%) asthmatics had a preserved FEV_1 > 80%, mean age: 40 years, FEV_1: 97%, median ICS dose: 800µg, 42% taking LABA, 22% on LTRA and 5% on theophylline. The proportion of patients at BTS treatment steps 1-4 were 6.3%, 37.7%, 27.8 % and 28.0 % respectively .The results in Table 1 showed that persistent small airways dysfunction, defined by FEF_{25-75} and R5-20, was associated with a significantly increased likelihood of having worse long-term asthma control. The risk of having poorer control was greater when measurements of FEF_{25-75} and R5-R20 were combined. However, adding in FEV_1/FVC to the model did not appreciably improve the OR compared to the combined outcome of FEF_{25-75} and R5-20 because FEV_1/FVC and FEF_{25-75} were both highly correlated ($r = 0.82$, $P < 0.001$). When our analysis was corrected for factors including age, gender, ICS, LABA and LTRA, the adjusted OR for FEF_{25-75} and R5-20 were similar. R5% predicted (n=302) and resonant frequency (n=268) however, did not have a significant impact in determining asthma control. There were insufficient evaluable data to perform a meaningful analysis on reactance area (AX) (n=75). During the study period, in those with a preserved FEV_1, there were a total of 14 Emergency Department visits and 33 hospital admissions for asthma exacerbations. However, these numbers were too small to perform a meaningful analysis.

Our results are similar to those of previously reported studies in asthmatic children by Shi et al [5] who showed a significant difference between selected cohorts of controlled and uncontrolled asthmatic children for both FEF_{25-75} and FEV_1/ FVC, while peripheral resistance (R5-R20 > 0.15 $kPa \cdot L^{-1} \cdot s$) and reactance area (AX > 0.95 $kPa \cdot L^{-1}$) were equally predictive for detecting control. In a prospective follow up study [6] of initially controlled asthmatic children, the same authors observed a significant difference in FEV_1/FVC but not FEF_{25-75} at baseline, but for both FEV_1/FVC and FEF_{25-75} at follow up after 3 months, comparing those who remained controlled to those who subsequently became uncontrolled. Rao et al [7] in a similar design to the present study over 2 years using electronic prescribing linkage, compared matched groups of asthmatic children who had a preserved FEV_1 (> 80%) with an abnormal FEV_1/FVC (< 0.85) and FEF_{25-75} (< 60%) versus those with normal values, showing significantly increased OR for loss of control in terms of oral steroid use, asthma exacerbations and controller use.

We elected to use cut-off thresholds for small airways measurements which provided the best compromise in terms of achieving balanced numbers of patients in each group from which to make informative comparisons. Such cut-off values for normality are always going to be rather arbitrary whether they are more of less severe in nature. We acknowledge our data has some limitations in terms of it being a retrospective type health informatics study linked to a single index measurement of pulmonary function. However, we feel that our data more closely reflects real life practice where compliance is usually poor in the community. Our unselected cohort of persistent asthmatics were referred from primary care and reflected a wide spectrum of severity across BTS treatment steps.

We feel that our study may have some important potential clinical implications. It appears that effort independent (i.e. IOS) and effort dependent measurements (i.e. spirometry) may provide distinct yet complimentary information on the small airways phenotype, as shown by

the higher OR for the composite of FEF_{25-75} and R5-R20 compared to either measurement alone.

It remains unclear as to whether small airway markers may be improved by using extra fine particle inhaled therapy including currently available extra fine ICS and ICS/LABA formulations and how this relates to long-term asthma control. We also do not know if small airways dysfunction as reflected by abnormal FEF_{25-75} or R5-20 is due to ongoing persistent inflammation or simply altered airways geometry. Several prospective randomised controlled trials have shown greater improvements in small airways outcomes in response to extra fine compared to coarse particle ICS formulations in unselected patient cohorts [8-12]. Other retrospective health informatics data comparing extra fine and coarse particle ICS formulations have revealed consistent results in terms of improved asthma control based on prescribing outcomes, but have not measured any small airway pulmonary function outcomes [13-15]. We believe the time has now come for designing prospective randomized controlled trials enrolling patients with an enriched small airways phenotype, perhaps powered on pragmatic outcomes such as the Asthma Control Questionnaire.

In conclusion, we have shown that in adult asthmatics who have a preserved FEV_1, the presence of persistent small airways dysfunction was associated with poorer control, perhaps suggesting the presence of a defined small airway asthma phenotype.

Table 1 Odds ratio (95% CI) for small airway indices in 302 patients with FEV_1 > 80% predicted

	Crude odds ratio	P value	Adjusted odds ratio	P value
FEF_{25-75} < 70 % n=157 versus FEF_{25-75} > 70% n=145				
Oral steroid use	1.67 (1.04-2.68)	0.04	1.50 (0.91-2.48)	0.11
SABA use	2.00 (1.27-3.16)	0.003	1.91 (1.19—3.07)	0.007
FEV_1/FVC < 0.80, n=167 versus FEV_1/FVC > 0.80, n=135				
Oral steroid use	2.06 (1.27-3.35)	0.004	1.85 (1.10-3.12)	0.02
SABA use	1.61 (1.02-2.54)	0.04	1.54 (0.95-2.51)	0.08
R5-R20 > 0.07 kPa·L^{-1}·s, n=135 versus R5-R20 < 0.07 kPa·L^{-1}·s, n =167				
Oral steroid use	1.99 (1.23-3.19)	0.005	1.80 (1.09-2.98)	0.02
SABA use	1.83 (1.16-2.89)	0.01	1.87 (1.15-3.01)	0.01
FEF_{25-75} < 70 % & R5-R20 > 0.07 kPa·L^{-1}·s; n=83 versus FEF_{25-75} > 70% & R5-R20 < 0.07 kPa·L^{-1}·s; n=93				
Oral steroid use	2.77 (1.48-5.18)	0.001	2.34 (1.20-4.58)	0.01
SABA use	3.07 (1.66-5.67)	<0.001	3.16 (1.64-6.07)	0.001
FEF_{25-75} < 70 % , R5-R20 >0.07 kPa·L^{-1}·s & FEV_1/FVC < 0.80; n=72 versus FEF_{25-75} > 70% & R5-R20 < 0.07 kPa·L^{-1}·s & FEV_1/FVC > 0.80; n=75				
Oral steroid use	3.29 (1.64-6.61)	0.001	2.78 (1.28-6.04)	0.01
SABA use	3.16 (1.61-6.19)	0.001	2.96 (1.44-6.12)	0.003

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