Small airway dysfunction is associated with poorer asthma control

To the Editor:

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 β-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) (assessed as the difference between the resistance at 5 Hz (Rs) and that at 20 Hz oscillation (R20)) and spirometry (assessed as the forced expiratory flow at 25–75% of forced vital capacity (FEF25–75%)) across British Thoracic Society (BTS) treatment steps for asthma, many of whom had a preserved forced expiratory volume in 1 s (FEV1). 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 airway dysfunction was associated with worse control in adult asthmatics with a preserved FEV1 (>80% predicted). Spirometry and IOS measurements from unselected asthmatics referred from primary care who attended screening for clinical trials were linked to prescription data. The prescription data were obtained from the Tayside Health Informatics Centre (Dundee, UK), 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 β-agonist (SABA) use. We evaluated whether small airway dysfunction, defined as FEF25–75% <70%, or peripheral airway resistance, defined as Rs-R20 >0.07 kPa·L⁻¹·s⁻¹, 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 more than four, or four or fewer SABA inhalers. Research ethics committee approval was obtained for all the studies for which the patients were being screened, and Caldicott Guardian approval was obtained to transfer the data to the Health Informatics Centre. IOS (Masterscreen IOS; Jaeger, Hochberg, Germany) was performed in triplicate in accordance with the manufacturer’s guidelines. A SuperSpiro spirometer (Micro Medical Ltd, Chatham, UK) was used in triplicate in accordance with European Respiratory Society guidelines [4]. Logistic regression analysis was applied to calculate the odds ratios for steroid and salbutamol use in the different groups. Age, sex, ICS, LABA and leukotriene receptor antagonists (LTRA) use were all included as covariates to calculate the adjusted odds ratio and 95% confidence interval.

302 (68%) out of 442 asthmatics had a preserved FEV1 (>80% pred) (mean age: 40 years; mean FEV1: 97% pred; median ICS dose: 800 µg; 42% were taking LABA, 22% were on LTRA and 5% were 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 show that persistent small airway dysfunction, defined by FEF25–75% and Rs-R20, 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 FEV1/FVC, associated with a significantly increased likelihood of having worse long-term asthma control. The results in table 1 show that persistent small airway dysfunction, defined by FEF25–75% and Rs-R20, 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 FEF25–75% and Rs-R20 were combined. However, adding in FEV1/FVC to the model did not appreciably improve the odds ratio compared to the combined outcome of FEF25–75% and Rs-R20 because FEV1/FVC and FEF25–75% were both highly correlated (r=0.82, p<0.001). When our analysis was corrected for factors including age, sex, ICS, LABA and LTRA, the adjusted odds ratios for FEF25–75% and Rs-R20 were similar. Rs % pred (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 of reactance area (Ax) (n=75). During the study period, in those with a preserved FEV1, 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 SII et al. [5] who showed a significant difference between selected cohorts of controlled and uncontrolled asthmatic children for both FEF25–75% and FEV1/FVC, while peripheral resistance (Rs-R20 >0.15 kPa·L⁻¹·s⁻¹) and Ax (>0.95 kPa·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 FEV1/FVC but
<table>
<thead>
<tr>
<th>FEF25–75% &lt; 70% (n=157) versus FEF25–75% &gt;70% (n=145)</th>
<th>Crude</th>
<th>Adjusted</th>
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</thead>
<tbody>
<tr>
<td>Oral steroid use</td>
<td>1.67 [1.04–2.68]</td>
<td>0.04</td>
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<td>SABA use</td>
<td>2.00 [1.27–3.16]</td>
<td>0.003</td>
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<tr>
<td>FEV1/FVC &lt;0.80 (n=167) versus FEV1/FVC &gt;0.80 (n=135)</td>
<td>Oral steroid use</td>
<td>2.06 [1.27–3.35]</td>
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<td>SABA use</td>
<td>1.61 [1.02–2.54]</td>
<td>0.04</td>
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<td>R5-R20 &gt; 0.07 kPa·L⁻¹·s (n=135) versus R5-R20 &lt;0.07 kPa·L⁻¹·s (n=167)</td>
<td>Oral steroid use</td>
<td>1.99 [1.23–3.19]</td>
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<td>SABA use</td>
<td>1.83 [1.16–2.89]</td>
<td>0.01</td>
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<td>FEF25–75% &lt;70% and R5-R20 &gt;0.07 kPa·L⁻¹·s (n=83) versus FEF25–75% &gt;70% and R5-R20 &lt;0.07 kPa·L⁻¹·s (n=93)</td>
<td>Oral steroid use</td>
<td>2.77 [1.48–5.18]</td>
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<td>SABA use</td>
<td>3.07 [1.66–5.67]</td>
<td>&lt;0.001</td>
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<td>FEF25–75% &lt;70%, R5-R20 &gt;0.07 kPa·L⁻¹·s and FEV1/FVC &lt;0.80 (n=72) versus FEF25–75% &gt;70%, R5-R20 &lt;0.07 kPa·L⁻¹·s and FEV1/FVC &gt;0.80 (n=75)</td>
<td>Oral steroid use</td>
<td>3.29 [1.64–6.61]</td>
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<tr>
<td>SABA use</td>
<td>3.16 [1.61–6.19]</td>
<td>0.001</td>
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FEF25–75%: forced expiratory flow at 25–75% of forced vital capacity; SABA: short-acting β-agonist; FVC: forced vital capacity; R5: resistance at 5 Hz; R20: resistance at 20 Hz.
not FEF25–75% at baseline, but for both FEV1/FVC and FEF25–75% at follow-up after 3 months, comparing those who remained controlled with those who subsequently became uncontrolled. In a similar design to the present study, over 2 years, using electronic prescribing linkage, Rao et al. [7] compared matched groups of asthmatic children who had a preserved FEV1 (>80% pred), an abnormal FEV1/FVC (<0.85) and FEF25–75% (<60%) with those with normal values, showing significantly increased odds ratios for loss of control in terms of oral steroid use, asthma exacerbations and controller use.

We elected to use cut-off thresholds for small airway measurements that 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 or less severe in nature. We acknowledge our data have some limitations in terms of this being a retrospective-type health informatics study linked to a single index measurement of pulmonary function. However, we feel that our data more closely reflect real life practice, where compliance is usually poor in the community. Our unselected cohort of persistent asthmatics was 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 airway phenotype, as shown by the higher odds ratio for the composite of FEF25–75% and Rs–R20 compared with 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 whether small airway dysfunction, as reflected by abnormal FEF25–75% or Rs–R20, is due to ongoing persistent inflammation or simply altered airway geometry. Several prospective randomised controlled trials have shown greater improvements in small airway outcomes in response to extra-fine compared with 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 randomised controlled trials enrolling patients with an enriched small airway 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 FEV1, the presence of persistent small airway dysfunction was associated with poorer control, perhaps suggesting the presence of a defined small airway asthma phenotype.

References

1 Lipworth B. Targeting the small airways asthma phenotype: if we can reach it, should we treat it? Ann Allergy Asthma Immunol 2013; 110: 233–239.

Conflict of interest: Disclosures can be found alongside the online version of this article at erj.ersjournals.com


