Lung elastic recoil and ventilation heterogeneity of diffusion-dependent airways in older people with asthma and fixed airflow obstruction

To the Editor:

Small airways are abnormal in asthma [1]. One measurement of small airway function is S_{acin}, derived from the multiple-breath nitrogen washout (MBNW) test. S_{acin} reflects ventilation heterogeneity in diffusion-dependent airways, and is correlated with airway hyperresponsiveness [2] and asthma control [3]. Theoretically, heterogeneity of diffusion-dependent ventilation can arise due to the heterogeneity of cross-sectional areas of airway openings in terminal airways and the acini [4]. Therefore, S_{acin} may be affected by structural changes in those airways. The elastic properties of the lung may also affect S_{acin}, as the phase III slope, a marker of ventilation heterogeneity derived from the single-breath nitrogen washout, correlates with lung compliance in explanted lungs of smokers and in healthy lungs [5].

Reduced lung elastic recoil makes a large contribution to airflow obstruction in asthma [6], particularly in older individuals who may develop fixed airflow obstruction (FAO). FAO typifies chronic obstructive pulmonary disease (COPD) but can occur in older asthmatics who have never smoked and despite adequate treatment [7, 8]. Since FAO is associated with age and S_{acin} is more abnormal in older asthmatics compared to younger [2], we hypothesised that the increase in S_{acin} in older people with asthma was due to loss of lung elastic recoil. Therefore, the aim of this study was to examine the relationships between S_{acin} and elastic recoil pressure and compliance.

We enrolled subjects from tertiary hospital clinics who were >40 years old, had ⩽5-pack-year smoking history and a physician diagnosis of asthma. To optimise asthma control, all subjects were treated with 2 months of maximal-dose inhaled corticosteroid (ICS)/long-acting β-agonist (LABA) using a fluticasone/eformoterol 250/10 µg metered-dose inhaler *via* a holding chamber, two puffs twice daily. Subjects completed the five-item Asthma Control Questionnaire (ACQ-5), standard lung function and MBNW (Exhalyzer D; ECO MEDICS AG, Duernten, Switzerland) as previously described [9], both during enrolment and after 2 months of treatment. Post-bronchodilator spirometry was performed after 1 month of treatment. S_{acin}, S_{cond} (ventilation heterogeneity in convection-dependent airways) and lung clearance index (LCI) (a global index of ventilation heterogeneity) were derived as previously described [10]. At the end of the 2-month treatment period, lung elastic recoil pressure was measured using an oesophageal balloon. The pressure–volume (P–V) curve was constructed from points obtained during five interrupted deflation manoeuvres from total lung capacity (TLC) to functional residual capacity (FRC). At least 30 acceptable points were plotted and an exponential function, $V=A-Be^{-KP}$, fitted to the P–V curve between 50% and 100% of TLC [11] using a least-squares fit, where V is volume, A is the horizontal asymptote, and B is the distance between A and the extrapolated y-axis intercept. The ratio of B/A, expressed as a percentage, is an index of lung elastic recoil; a low ratio indicates reduced lung elastic recoil (leftward shift of the P–V curve). K is an index of the curvature of the exponential relationship between P and V. Increased K indicates a steeper P–V curve at lower lung volumes near FRC (hence, increased compliance) but a flatter slope at higher lung volumes (hence, lower compliance near TLC). K is thought to represent the lung's elastic properties better because it takes into account lung volume over a meaningful range, as

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opposed to chord compliance, which only takes into account the linear portion of the *P–V* curve. Lung elastic recoil does not change post-bronchodilator in stable conditions [12] and the measurement is invasive; therefore, post-bronchodilator *P–V* measurements were not performed. ICS/LABA and short acting β-agonist medications were withheld for at least 24 and 6 h prior to testing, respectively. Correlations between pre-bronchodilator MBNW and *P–V* indices were assessed using Spearman's rank test.

21 subjects were enrolled; three could not complete the study. All subjects were taking an ICS with or without LABA; five subjects were also taking a long-acting muscarinic antagonist. One subject was on long-term low-dose oral corticosteroids (prednisone dose 5 mg) for rheumatoid arthritis. Five subjects were ex-smokers (mean±SD history 2.2±2.5 pack-years). The mean±SD age was 64.1±8.0 years, height 1.69 ±0.10 m, body mass index 28.4±6.0 $kg \cdot m^{-2}$, asthma duration 38.9±22.5 years and ACQ-5 score 1.07±0.92. Post-bronchodilator spirometry after 1 month of treatment showed moderate FAO: mean±SD z-score forced expiratory volume in 1 s (FEV_1) −2.2±0.5, forced vital capacity (FVC) −0.7±1.0 and FEV_1/FVC −2.6±0.7. After 2 months, spirometry did not change; there was mild gas trapping (residual volume z-score 2.0±1.6) and mildly reduced diffusing capacity of the lung for carbon monoxide (78±15% predicted). All MBNW indices were higher than normal and also did not change after 2 months of treatment: median (interquartile range) z-score S_{cond} 3.3 (3.1–4.2) L^{-1}, S_{acin} 2.8 (2.1–3.8) L^{-1} and LCI 4.6 (2.3–7.8). *P–V* curves were generated from TLC to a lower limit volume of 55% (51–60%) of TLC. Lung elastic recoil was lower (*B*/*A*% z-score $\leqslant -1.64$) in five out of 18 subjects and compliance was higher (*K* z-score $\geqslant 1.64$) than normal in nine out of 18 subjects. Elastic recoil pressure at functional residual capacity was low at 1.4 (0.8–3.6) cmH_2O.

Increasing age was associated with reduced lung elastic recoil (*B*/*A*% $r_s=-0.52$, p=0.02) and increased lung compliance (*K* $r_s=0.50$, p=0.04) but not with MBNW indices. Increased S_{acin} and LCI were both associated with loss of lung elastic recoil, *B*/*A*% ($r_s=-0.53$ (p=0.03) and $r_s=-0.52$ (p=0.03), respectively) (figure 1). There were no associations between S_{cond} and *B*/*A*% ($r_s=0.28$, p=0.3), or between any MBNW indices and lung compliance (*K*: $r_s=0.18$ (p=0.5), $r_s=0.002$ (p=1.0) and $r_s=0.33$ (p=0.2) for correlations with S_{acin}, S_{cond} and LCI, respectively).

This study shows that in asthmatics over the age of 40 years with FAO, uneven ventilation distribution in diffusion-dependent airways was associated with reduced lung elastic recoil but not with increased lung compliance. Convection-dependent ventilation distribution was unrelated to either lung elastic recoil or compliance. Furthermore, despite maximal ICS/LABA treatment, lung function did not change over a 2-month period, suggesting a steroid-unresponsive process. These findings suggest the mechanical properties of the lung parenchyma are an important determinant of peripheral airway function in older people with asthma and FAO.

We used *B*/*A*% as an index of reduced elastic recoil pressure. *A* approximates TLC, whereas *B* is the volume spanned by the *P–V* curve, in turn related to shifts in recoil. Therefore, *B* decreases when recoil pressures decrease, *i.e.* the curve is shifted to the left [13]. Since TLC was normal in our subjects, the signal in elastic recoil changes arises from *B*: *versus* S_{acin}, $r=-0.43$ (p=0.08) and *versus* LCI, $r=-0.52$ (p=0.03). *B*/*A*% then normalises for TLC. Reduced *B*/*A*% indicates that recoil pressures generated by alveoli and intra-acinar airways is reduced, and that the lung and acinar airways, which then reach full inflation at lower distending pressures compared with normal lungs, *i.e.* greater distensibility. Decreasing *B*/*A*% with age explains the increase in closing volume and residual volume/TLC with increasing age [13]. The lack of relationship between S_{acin} and *K* suggest that airspace *per se* is not a determinant.

If reduced lung elastic recoil due to asthma is variably distributed throughout the lungs, then alveolar and intra-acinar airway sizes would be more variable. Thus, S_{acin} would increase since regional specific ventilation, which is determined by alveolar size and cross-sectional areas of the intra-acinar airway openings [4], would become more heterogeneous too. A global loss of elastic recoil could also increase overall ventilation heterogeneity, by amplifying normal airway structural asymmetry and/or by bringing some airways towards closure, thus changing airway closure distribution.

Support for heterogeneous distribution of lung tissue changes has been demonstrated in *post mortem* asthmatic lungs from nonsmokers [8]. Microscopic examination confirmed mild, diffuse centrilobular emphysema-like changes, predominantly in the upper to middle lobes, as well as areas of normal lung parenchyma. The variability in the histopathological abnormalities within an asthmatic lung suggests the distribution of lung elastic recoil pressures will also be distributed heterogeneously, thereby increasing ventilation heterogeneity. Age-related structural changes such as enlargement of the airspaces, alveolar wall thickening and reduced number of peripheral airways [14] may also be distributed unevenly. These age-related changes may explain the rapid increase in ventilation heterogeneity values beyond 60 years of age [15]. In this study, age was associated with both *B*/*A*% and *K*, consistent with the known relationship in healthy individuals. It is possible that there is an interaction between asthma-related changes in lung

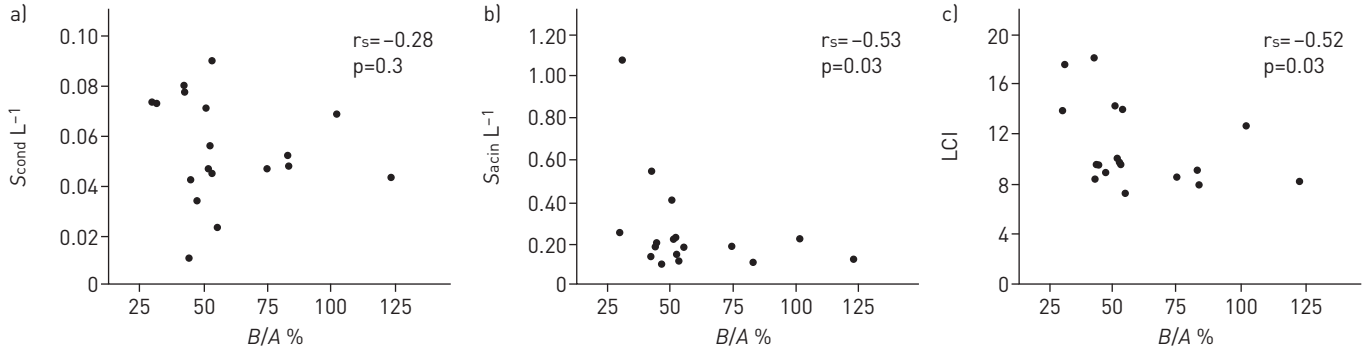

FIGURE 1 Univariate correlations (Spearman test) between multiple-breath nitrogen washout indices and lung elastic recoil (*B/A*): a) S_{cond} (ventilation heterogeneity in convection-dependent airways); b) S_{acin} (ventilation heterogeneity in diffusion-dependent airways); c) lung clearance index (LCI), a global index of ventilation heterogeneity.

and airway structure and ageing, which alters the lungs elastic properties and small airway structure in a highly variable manner. Hence, asthma and ageing could have interactive effects on the elastic properties of the lungs. A weakness of this study is that we are unable to examine any potential interactions of ageing as a potential mechanism for the relationship between S_{acin} and *B/A*%. This is because age was unrelated to S_{acin} (p=0.43), possibly related to the small numbers and narrow age range in this study.

In summary, we found that a loss of elastic recoil, but not lung compliance, was associated with increased ventilation heterogeneity in diffusion-dependent airways in older asthmatics with FAO. The mechanisms causing loss of lung elastic recoil in asthma need further investigation as they may provide insight into causes of small airway dysfunction in asthmatics who develop FAO despite negligible smoking history. This may represent a potential pathway by which the asthma–COPD overlap phenotype is manifest and therefore highlights the need for development of novel treatments that target loss of elastic recoil in asthma.

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This study is registered at www.anzctr.org.au with identifier number ACTRN12615000985583. The data sets generated and/or analysed during the study are available from the corresponding author on reasonable request.

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Conflict of interest: K.O. Tonga has nothing to disclose. N. Berend reports that he is a part-time employee of and holds shares in GlaxoSmithKline outside the submitted work. C. Thamrin has nothing to disclose. C.S. Farah has nothing to disclose. K. Jetmalani has nothing to disclose. D.G. Chapman has nothing to disclose. G.G. King has nothing to disclose.

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