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Title: Repeatability and inter-relationships of small airway biomarkers in asthma

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Body: Background: There is evidence that small airway dysfunction may have an important role in asthma. We aimed to determine the within-visit and between-visit repeatability of small airway biomarkers in asthma, and explore the inter-relationships between them and with standard pulmonary function tests. Methods: We recruited ninety-eight patients with asthma. All participants attended a baseline visit at which they undertook spirometry, body plethysmography, measurement of carbon monoxide diffusing capacity, impulse oscillometry (IOS), multiple breath washout (MBW) and induced sputum cell count. Eighteen patients undertook two-week and three-month follow-up visits, and twenty-six patients undertook six-month follow-up visits, at which all physiological tests were repeated. Results: Small airway biomarkers displayed excellent within-visit repeatability (intraclass correlation coefficient [ICC] > 0.9), with the exception of S_{cond}, which was only moderately repeatable (ICC = 0.629). The biomarkers were all very stable over a three-month time frame, but S_{cond} and S_{acin} were only moderately stable over six months. Principal components analysis of the variables derived five components, corresponding to the concepts of: 1) Expiratory flow limitation / air trapping 2) Heterogeneous airway constriction / closure 3) Ventilation heterogeneity 4) Airway inflammation 5) Impaired diffusion capacity Conclusions: Small airway biomarkers are repeatable and stable over three months. Moreover, they appear to provide additional and independent physiological information over and above standard pulmonary function tests.