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Title: Clinical significance of ventilation heterogeneity in adult patients with asthma

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Body: Background Ventilation heterogeneity (VH), measured using multiple breath inert gas washout (MBW), is thought to be a sensitive marker of small airway obstruction. We hypothesised that VH would be (i) associated with impaired asthma control and reduced quality of life in patients with normal spirometry, (ii) related to asthma severity, and (iii) differentially expressed across clinical asthma phenotypes. Methods Ninety-one patients with asthma and eighteen healthy control subjects attended a single visit and underwent clinical and physiological characterisation, including spirometry, body plethysmography, impulse oscillometry, MBW and induced sputum cell count. Patients completed the six-point Asthma Control Questionnaire (ACQ-6), Asthma Quality of Life Questionnaire (AQLQ) and visual analogue scores for cough, breathlessness and wheeze. Results Among those with normal spirometry, asthma patients with increased VH manifested increased ACQ-6 scores (1.48 vs 1.03, $p < 0.05$) and reduced AQLQ scores (5.20 vs 5.74, $p < 0.05$) compared to those without increased VH. Acinar VH was significantly increased in patients with severe asthma compared to healthy controls (Mean $S_{\text{acin}(\text{corr})} = 0.211$ vs 0.114, $p < 0.01$). VH parameters did not differ between the four clinical phenotypes examined, and were not associated with markers of eosinophilic airway inflammation. Conclusions VH is associated with impaired asthma control and reduced quality of life in patients with normal spirometry. Further studies are required to determine whether VH parameters may be utilised to predict the risk of fixed airflow obstruction in asthma and stratify the response to small particle inhaled and systemic asthma therapies.