Title: Comparison of measures of ventilation heterogeneity derived from multiple breath inert gas washout

Body: Introduction: Multiple breath inert gas washout (MBW) is a technique for quantifying ventilation heterogeneity (VH). We compared four measures of VH with regard to repeatability, ability to discriminate between healthy subjects and patients with asthma, and robustness to variations in tidal volume (Vt), anatomical dead space (Vd) and functional residual capacity (FRC). Methods: MBW was performed in triplicate on 13 healthy subjects and 22 patients with moderate to severe asthma, using a previously published method (Horsley et al. Thorax. 2008; 63(2): 135-140). Lung clearance index (LCI), mixing ratio (MiR) and moment ratio (MoR) were calculated. A novel marker of VH, the rate constant ratio (RCR), was calculated by fitting the washout data to a two-phase decay model and calculating the ratio between the fast and slow rate constants. Repeatability and discriminatory ability were assessed using intraclass correlation coefficients (ICC) and receiver operating characteristic (ROC) curves, respectively. Robustness of the parameters was assessed by calculating the signal-to-noise ratio (SNR), using simulated MBW data to determine the noise caused by variations in FRC, Vt and Vd. Results: LCI, MoR and MiR exhibited good repeatability, with ICC values of 0.899, 0.888 and 0.885 respectively, but RCR was less repeatable (ICC = 0.783). The parameters all had areas under the ROC curve between 0.7 and 0.75. The most robust parameter was the RCR (SNR = ∞), followed by the MiR (SNR = 6.8), LCI (SNR = 3.4) and MoR (SNR = 1.2). Conclusion: MiR appears to be the most favourable measure of VH. We recommend that it is reported alongside the LCI.