Comparison of global multiple breath washout measured at the mouth to imaging multiple breath washout in healthy subjects and CF patients.

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Target audience: hyperpolarised MRI, Lung MRI, multiple breath washout**;**

Purpose: Multiple breath inert gas washout as measured in the pulmonary function lab (MBW) is a technique thought to be sensitive to early signs of ventilation heterogeneity in obstructive lung diseases like CF [1]. By measuring signal intensity decay during MBW using hyperpolarised gas MRI this method has been extended to a regional measure of MBW [2,3]. The objective of this work is to compare the results of gas washout measured with 3D HP-MRI (MBW-I) to MBW with the aim of better understanding ventilation heterogeneity in the context of a global MBW test.

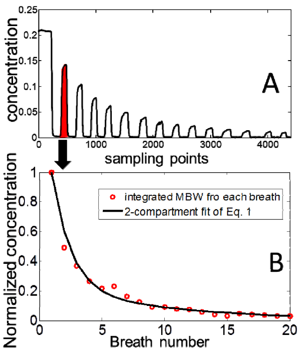

Figure 1: Multiple breath washout as recorded in the pulmonary function lab (MBW) from CF patient 1. (A) Tracer gas concentration (Note: Tracer gas can only be detected during exhalation during washout). (B) Integrated concentration decay and least-squares fit to Eq. 1.

Materials and Methods: Both MBW-I and MBW were performed on 4 healthy volunteers (age 20±11 years, 3 females) and 3 patients with moderate CF (age 15±2.4 years, 2 females). All subjects had a normal forced expiratory volume in 1 second (FEV1) of >80%. **MBW:** A gas analyser was used to perform MBW according to guidelines [4]: Following a wash in of 0.2% SF_6 gas to equilibrium concentration, washout was monitored over multiple breaths (Fig. 1A). MBW was performed supine to replicate the position during MBW-I. Exhaled tracer gas concentration was integrated for each breath (Fig 1B-red circles). **MBW-I:** Multiple breath washout imaging was performed on a 1.5T scanner with a quadrature ^{3}He flex coil. A gas mixture of ^{3}He (~20% polarisation, 150-300ml, depending on height and weight) topped up with N_2 was inhaled. Two 3D volumes were acquired at breath-hold to correct for RF depolarisation and T_1 decay (assuming constant T_1 during the experiment). The next three image volumes were acquired during washout with tidal breathing at a fixed interval (4s) as shown in Fig. 2A (images) and Fig. 2B (volume-time curve). The images were segmented and motion-corrected [5] before calculating fractional ventilation *r* on a voxel-by-voxel basis (Fig.2C). Fractional ventilation *r* was normalized by tidal volumes recorded during MBW and MBW-I. **Comparison:** The MBW curve was fitted with a model assuming 2 functional lung compartments with different fractional ventilation *r* as well as different volume V (Fig 1B – black line) [6] using Eq. 1. Note we assume an equilibrated gas concentration throughout the lungs at the start of the experiment. Since exhaled gas is measured at the mouth by MBW rather than residual gas, as in MBW-I, a value of (1-*r*) is expressed in Eq. 1 for the two assumed compartments. The MBW-I fractional ventilation map was then divided into two volume fractions (Fig. 2C) using the volume fraction (V) from fitting the MBW curve with Eq.1. The mean imaging fractional ventilation values for each volume segmented according to this compartmental threshold was then compared to the corresponding r_1 and r_2 from the MBW-fit. To statistically measure the agreement of the MBW-I and MBW methods Bland-Altman analysis was performed. (Fig2C).

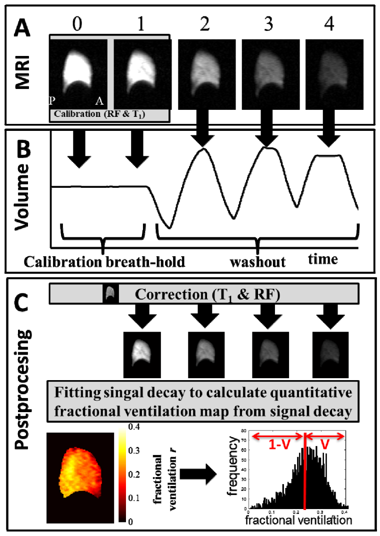

Figure 2: Diagram of MBW-I. MRI acquisitions during washout (A), acquired together with breathing pattern (B). (C) From images fractional ventilation maps can be calculated . A histogram is used to get mean fractional ventilation for 2 compartments.

$$C_{global}(n) = (1 - r_1)^{n-1} \cdot V + (1 - r_2)^{n-1} \cdot (1 - V)$$

Eq. 1: $C_{global}(n)$ is the measured concentration during MBW at the mouth at breath *n*. In this case the lung is split into two compartments with fractional ventilation *r* and different size *V (fraction of total lung volume).*

Results: The Bland-Altman plot in Fig.2 shows the comparison of the two compartments with the corresponding measured average values from fractional ventilation maps for all compartments and experiments. All values are well within 1.96 standard deviations. The Bland-Altman plot shows a slight tendency of MBW-I to overestimate low values of *r* and underestimate values of high *r*. Despite the young age of the subjects all could follow instructions during MBW-I after one training acquisition.

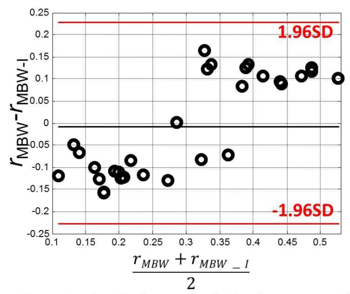

Figure 3: Bland-Altman analysis of MBW-I and MBW fractional ventilation values. Pearson's correlation coefficient R = 0.83 (P<0.001).

Discussion: Comparing the methods with a two compartment model with Bland-Altman analysis shows an agreement between MBW and MBW-I. In this preliminary work a 2-compartment model was chosen, which might explain the skewed trend of correlation of mean value to difference in the Bland-Altman plot. For future work it is expected that models with more compartments would show better agreement between MBW and MBW-I particularly in more obstructed lungs. Despite the argument that MBW-I (unlike MBW) is performed after only a single breath wash in, it has been shown that the gas equilibrates on a timescale of seconds during the calibration breath-hold [7]. The different diffusion constants of ^{3}He and SF_6 are almost negligible when considering tracer gas volumes (<10% ^{3}He in total lung volume during the first breath-hold and 0.2% SF_6). If the diffusivity of the gas mixture is of interest the MBW-I could indeed be performed with a heavier gas such as ^{129}Xe [8] or SF_6.

Conclusion: MBW-I is shown to provide similar information on gas washout as MBW when a 2 compartment model is used. The regional fractional ventilation provided by MBW-I gives unique spatial insight into the washout time constants (*r*) of the whole lung, and may help understanding the concept of ventilation heterogeneity in the context of clinical MBW measurements made from the whole lung. In this preliminary study we have shown that fractional ventilation maps from ^{3}He-MRI washout images are comparable to conventional MBW, an important pre-requisite for the subsequent regional interpretation of ventilation heterogeneity that MBW is thought to be sensitive to.

References: [1]Aurora, Thorax(2010), 65(5), 373-74; [2]Deppe et al., ISMRM proceedings, 2011; [3]Horn et al., ISMRM proceedings, 2013; [4] Robinson et al., European Respiratory Journal, 2013, 41(3), 507-22; [5] Barber et al.; Med Image Ana.(2007), 11(6), 648-62; [6]Fuller et al.(1990),11(2), 149-58; [7] Marshall et al., Thorax(2012),67(7),613-7; [8] Horn et al., ISMRM proceeding 2012;

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