Quantitative Multi-Breath Fractional Ventilation Imaging in Voluntarily Breathing Humans

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INTRODUCTION: Pulmonary ventilation is a key marker for diagnosis and monitoring progression of obstructive lung diseases – especially in heterogeneous pulmonary conditions – and its noninvasive imaging can provide useful information to investigate the severity of disease and patient's response to therapeutic interventions. Hyperpolarized (HP) gas MRI provides a noninvasive platform to directly image distribution of respiratory gas in the acinar airways at a high spatial resolution. Quantitative imaging of ventilation however still remains as one of the least developed areas in this field and using this imaging modality. A technique for quantitative imaging of fractional ventilation (r) was developed and implemented in mechanically ventilated animals [1], and further improved with provisions to enable implementation in large species (with lungs volumes comparable to humans) [2]. Extension of the proposed technique to human subjects was complicated by the requirement for administration of a series of identical HP gas breaths (simultaneously with oxygen) while acquiring the images after each breath at the same point in respiratory cycle. This work presents for the first time the feasibility of performing such measurements of fractional ventilation imaging in voluntarily breathing human subjects using a passive-reactive HP gas mixing and delivery device.

METHODS: The basic requirement of the utilized fractional ventilation (r) imaging method is administration of a series of identical normoxic HP gas breaths to the subject, while images are acquired during a short end-inspiratory breath-hold. Signal buildup of HP gas in the airways is then fit to a recursive model and solved for r on a regional basis. Extension to consciously breathing humans was enabled by a passive-reactive respiratory gas mixing and administration device that allowed delivery of HP gas over a series of breaths at the prescribed volume and synchronized breathing pattern with image acquisition (design details described in another abstract submitted to this conference). Mixtures of HP ^{3}He-N_2 and O_2-N_2 were prepared in two separate bags (2.1 L each, ^{3}He:N_2:O_2≈25:55:20) administered over 6 breaths (I:E~3:4, ~10 BPM), while monitoring SpO_2, HR, BP and RR. MRI was performed in a 1.5-T Sonata (Siemens Healthcare) using an 8-channel chest coil (Stark Contrast) and GRAPPA ~2× acceleration (5×22-mm coronal slices, 4-mm spacing, ~6×6mm^2 spatial resolution, FOV=40×30cm^2, α=~5°, TR/TE=3.6/3.3). Two volunteers underwent the feasibility studies: a 25-yr old healthy male (V_T=700, BMI=19.6), and a 69-yr old active smoker (60 pack-yrs, V_T=750mL, BMI=25.0, FEV_1/FVC=0.61, FEV_1=62% pred.), suspected as a stage II COPD.

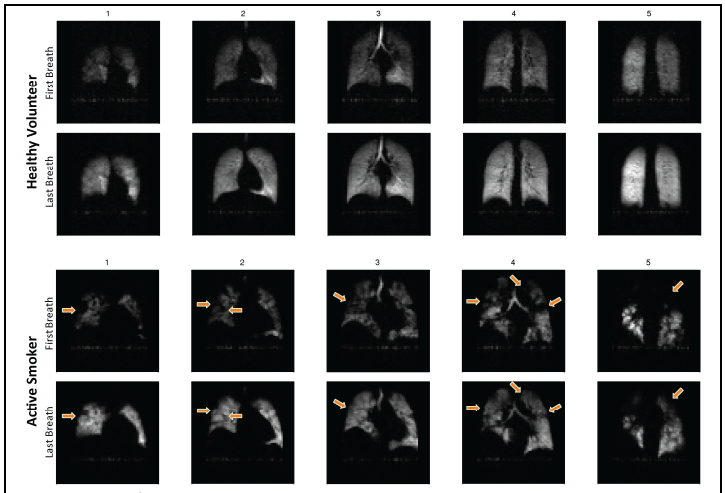

Figure 1. HP ^{3}He spin density images corresponding to the five coronal slices from the first and last breath of the serial fractional ventilation imaging sequence for both subjects.

RESULTS & DISCUSSION: Representative coronal ^{3}He density images from the lungs of the healthy and smoker subjects are shown in **Figure 1**. Images corresponding to the first and the last (6th) breaths in the sequence are shown for all five coronal slices. The SNR in the last image ranged over 50–70 given the continuous administration of oxygen during the study. It is evident that apart from the overall signal intensity, the two image sets are qualitatively the same for the healthy subject. The first important observation – and possibly somewhat different from single-breath ventilation images reported before – is that the distribution of gas in the smoker is drastically different between the first and last breath. Numerous regions in the smoker's lung (noted by *arrows* in **Figure 1**) exhibit nearly no signal in the first image, while the respiratory gas eventually finds its way to after several breaths, indicating a heterogeneous distribution time constant and likely an air trapped region. On the contrary there are a number of areas (mostly peripheral and apical) in this lung that even after several breaths remain inaccessible by the respiratory gas, likely indicating pulmonary shunt or severe obstruction. The corresponding quantitative maps of r are shown in **Figure 2**, overlaid on corresponding ^{1}H images of thorax (albeit not perfectly overlaid). Fractional ventilation distribution is fairly uniform in the parenchyma of the healthy subject's lung. High r values are observed in trachea and major bronchi as expected. An area near the heart shows an artificially high value likely due to motion artifacts. The r distribution is a lot more heterogeneous in the smoker's lung as suspected. An interesting observation is that regions which are in the proximity of gross ventilation defects (as judged from spin density images in **Figure 1**) exhibit an unusually high r value. At the same time the regions which slowly become visible in transition from the first to last breath, show a proportionally low r value. This observation is likely due to the transport of gas between the well-ventilated and poorly-ventilated regions, and the fact that this distribution takes place at different time constants among various regions in the lung, especially those afflicted by airway obstruction, air trapping, or pulmonary shunt.

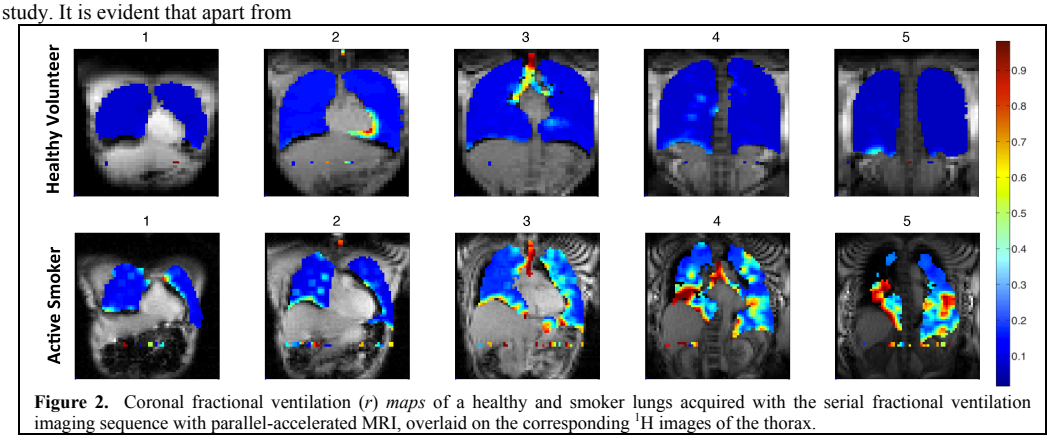

Figure 2. Coronal fractional ventilation (r) *maps* of a healthy and smoker lungs acquired with the serial fractional ventilation imaging sequence with parallel-accelerated MRI, overlaid on the corresponding ^{1}H images of the thorax.

CONCLUSION: The feasibility of performing multi-breath fractional ventilation MRI with HP ^{3}He in human subjects was demonstrated in this study. This methodology is the first to report a quantitative measure of respiratory gas distribution and replacement in human lungs. The translation of this imaging technique to humans was enabled by a combination of a gas mixing and delivery device which not only titrated the administered the prescribed tidal volume per breath, but also maintained a normoxic gas mixture throughout the study, queued the patient for committing intermittent breath-holds and eliminated operator intervention and subsequent errors associated with it. The detailed mechanisms of gas transport in lungs with heterogeneous ventilation defects require further investigation to explain the reflections on r values before proper interpretation can be made. Additionally repeatability of these measurements needs to be evaluated through a series of systematic experiments. Prior evaluations of this methodology in mechanically ventilated animals indicated a fairly good reproducibility given an accurate and repeatable volume administration protocol. Fractional ventilation can now therefore be evaluated as a marker to investigate heterogeneous obstructive lung diseases.

REFERENCES: [1] Denninger AJ *et al.*, *Magn Reson Med*. 2002 Aug; 48(2):223-32; [2] Emami K *et al.*, Magn Reson Med. 2010 Jan; 63(1):137-50. [3] Emami K *et al.*, *NMR Biomed.* 2011 (in press); [4] Griswold MA *et al.*, Magn Reson Med. 2002 Jun;47(6):1202-10.