Regional MR correlations of lung function and structure in a Rat model of emphysema using hyperpolarized 3He MRI

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INTRODUCTION: Conventional methods to diagnose and evaluate emphysema include global markers measured by pulmonary function tests (PFTs). Lung diffusion MRI with hyperpolarized (HP) 3He gas has emerged in the past decade as a technique allowing regional changes in lung structure and function induced by pulmonary disease, such as emphysema, to be detected earlier, thus facilitating the evaluation and monitoring of the progression of the disease. However, the relationship between conventional PFT markers to MRI regional lung structure and function measurements has not been well characterized. The MRI measurements we measure are alveolar size by the apparent diffusion coefficient (ADC) and fractional ventilation (r). In this study we will examine correlations between these regional HP 3He MRI measurements as well as validating our method by studying their behavior and sensitivity when compared to a number of global functional PFT markers in both healthy and emphysematous rats. Relationships between PFT and MRI measurements improve our understanding of how function and structure evolve in the presence of emphysema and strengthens the argument that HP 3He MRI techniques give us the same if not better diagnostic information as current clinically accepted methods.

METHODS: All experiments were conducted in accordance to an approved IACUC protocol. Global and regional measurements of lung function and structure were studied in two cohorts (1) 4 healthy controls and (2) 4 severely emphysematous rats. Emphysema was induced in male Sprague-Dawley rats by a single intratracheal instillation of 22U/100g of porcine pancreatic. The healthy cohort, with similar physiological conditions was kept in the same environment. At 14 months after elastase induction, both cohorts underwent standard pulmonary function tests performed using a plethysmographic maneuver system (Buxco Electronics). PFT was followed within 7 days by MRI session during which r and ADC of ^{3}He were measured in phase encode (PE) direction with the middle slice being examined. For imaging, rats were intubated using a 14-gauge angiocatheter and induced with ketamine and xylazine anesthesia, temporarily paralyzed with pancuronium bromide, and ventilated using an MRI compatible ventilator, while vital signs being monitored at a tidal volume = 15% TLC, 60 BPM and I:E=1:2. Imaging was performed on a small-bore 4.7-T animal scanner (Varian Inc., Palo Alto, CA) using a home-made 12-leg birdcage coil tuned to ^{3}He frequency of 152.95 MHz. HP ^{3}He was generated via spin-exchange optical pumping method using a commercial polarizer (GE Healthcare, Durham, NC). Helium images were obtained during a breath-hold using a multi-slice gradient echo imaging pulse sequence with the following parameters: FOV=6x6cm^2, number of slices=3, slice thickness=6mm, inter-slice gap=0.5mm, flip angle=4~5°, matrix size=64x64 pixels, T_R=4.1ms, and T_E=2.1ms. Diffusion images were acquired using a diffusion-weighted gradient echo pulse sequence with diffusion time Δ=1ms, and *b*-values = *0.00, 3.41, 2.00, 0.91, and 0.00 s/cm*^{2}. Fractional ventilation was measured using incremental build-up of HP ^{3}He signal in the lung by acquiring an image at the end of each polarized gas breath as described in *Emami et al. [1],* for 10 HP breaths. Data analysis was performed using Matlab.

Figure 1

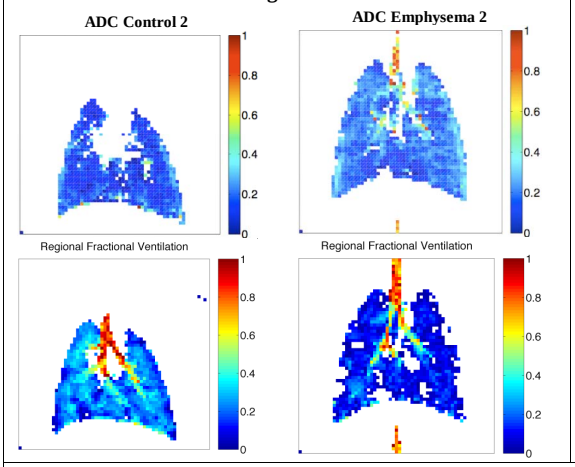

Figure 2

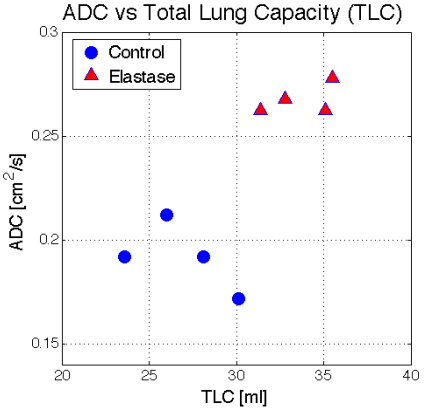

Table 1

Correlations
ADC-Cdyn
ADC-TLC
ADC-FEV/FRC
ADC - r
r-FEV/FRC
r-Cdyn
r-RI

a.

Marker	Average % difference	% overlap
r	-51	0
ADC	39	0
Cdyn	29	27
FEV/FRC	-26	51
TLC	25	0
RI	-16	50

b.

c.

Marker		p-value
ADC	Apparent diffusion coefficient (cm^2/s)	1.52E-04
TLC	Total lung capacity (ml)	0.0076
r	Fractional ventilation	0.0125
Cdyn	Lung compliance (ml/cm H_2O)	0.0669
RI	Lung resistance (cm H_2O*secs/ml)	0.0758
FEV_{50}/FRC	Forced expiratory volume (50ms)/ Functional residual capacity)ml	0.1927

Figure 1. Representative maps of ADC and fractional ventilation (r). **Figure 2.** Comparison between ADC and TLC; **Table 1a.** Correlations plotted in this study**; 1b.** Percent overlap and average percent difference between elastase and control groups with respect to the control group; **1c.** Student's t-test statistical significance of the difference between mean values of control and elastase groups (p<0.05).

RESULTS AND DISCUSSION: Figure 1 shows representative maps of ADC and fractional ventilation for a healthy and an elastase animal. A threshold-based metric was utilized to segment the distribution of ADC (cutoff = 0.15cm^2/s) and fractional ventilation (cutoff =0.015) values in the lung [2]. Fractional ventilation values were normalized to the FRC. Threshold values for each animal were plotted against PFT measurements of interest (see Table 1a.). An example is shown in Figure 2. where threshold ADC values are compared to measured TLC. We observe distinct clusters which correspond to the control and elastase groups. Table 1b shows the percentage overlap and the average percent difference of each parameter in the elastase group with respect to the control group. In Table 1c, a Students's t-test with p<0.05 shows that the mean values of ADC, TLC and fractional ventilation all differ significantly between control and elastase groups (in fact, no overlap is seen between the groups). In contrast, there was no significant (p<0.05) separation between control and elastase groups for lung resistance, lung compliance and FEV(50ms)/ FRC, although the latter two metrics do differ between the groups at a higher significant level. Although COPD and emphysema are often characterized by an increase in lung resistance, this metric does not differ between the groups, perhaps because the limited fidelity of the animal model and in particular the lack of applicability to chronic bronichitic forms of COPD. In general, the measurements conform to the expected relationships between MR regional measurements and PFT measurements between groups [3] (with the exception of lung resistance as described above), although we observe better clustering and less overlap using MR measurements compared to the corresponding PFT measurements.

ADC and r maps (not shown) were aligned using 2D rigid registration to correct for image misalignment due to moving the animal between the two acquisitions in order for the gas chamber to be refreshed. Scatter plots of ADC vs fractional ventilation on a pixel by pixel basis for each animal do not show consistent correlation between the two measurements. Difference in gradients of lines of best fit could not be effectively used to distinguish between control and elastase groups.

CONCLUSION: Preliminary results show that regional MRI measurements, ^{3}He ADC and fractional ventilation, are more sensitive to elastase-induced changes in rat lungs than the examined PFT measurements. Purely regional MRI analyses does not allow clear discrimination between healthy and elastase cohorts.

REFERENCES: [1] Emami K, *et al.* A novel Approach to Measure Regional Lung Ventilation Using Hyperpolarized 3He MRI – Potential in Clinical Studies; ISMRM 16th Scientific Meeting, Berlin, German: May 2007

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[3] Matthew L, *et al.* Hyperpolarized 3He Magnetic Resonance Imaging of Chronic Obstructive Pulmonary Disease: Reproducibility at 3.0 Tesla. Academic Radiology, Vol 15, No10, October 2008