Assessment of Regional Alterations of Lung Function and Structure by Hyperpolarized 3He MRI in a Murine Model of Emphysema

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INTRODUCTION: Chronic obstructive pulmonary disease continues to have a high morbidity rate and is among the 4 leading causes of death in the US. Noninvasive methods capable of visualizing structural and functional changes in the lung have a great potential for assisting diagnosis and therapeutic monitoring of this and other pulmonary disease. Hyperpolarized ^{3}He MRI as a non-invasive imaging technique has demonstrated sensitivity to airway remodeling. In this work we assess the sensitivity of two HP ^{3}He MRI-based measurements of gas diffusivity and ventilation to elastase-induced changes in a murine model of emphysema. The motivation is primarily the increasing interest in assessment of pulmonary disease models, and in assessment of therapeutic interventions in transgenic murine disease models, thereby making it necessary to extend functional and structural lung imaging techniques to a smaller scale.

METHODS: A group of 12 male Balb/c mice (3~4 month old; 26±2 g body weight) were divided into two cohorts: (1) 6 healthy controls; (2) 6 elastase-induced emphysematous. Animals were sedated with 100 mg/kg IP ketamine and 10 mg/kg xylazine and tracheotomy was performed with a 1.5-mm ET tube. Saturation level of blood oxygen, heart rate and temperature were continuously monitored during the study. Mice were mechanically ventilated with a V_T of 1.2 ml/100 g body weight at 110 BPM and I:E=1:2 with breathing air. For imaging the ventilation gas was switched to a mixture of ^{3}He:O_2 (4:1) with identical ventilation parameters. Imaging was performed on a 50-cm 4.7-T MRI scanner equipped with 12-cm 25 G/cm gradients. A ∅1" surface coil (152.95 MHz) with adjustable orientation was placed on top of the chest, while the mice were placed supine in the magnet. Single-slice images were acquired using a fast gradient echo pulse sequence with the following parameters: FOV=3×3cm^2, THK=4mm, α=20° (r) and 45° (ADC), MS=64×64 pixels (planar resolution of ~470 µm). Fractional ventilation was measured as described earlier [1]. ADC images were obtained using a DW-GEMS imaging pulse sequence with Δ = 1 ms, and b-values = 0.0 and 2.18 s/cm^2 along the phase encoding direction. Pulse width calibration was performed on the loaded RF coil to estimate the applied flip angle for each animal. For statistical analysis a significance level of 0.05, moderate effect size of 0.5, and a statistical power of 80% were used. A separate one-way ANOVA test was performed for analysis of variance of fractional ventilation and apparent diffusion coefficient between the two cohorts of mice.

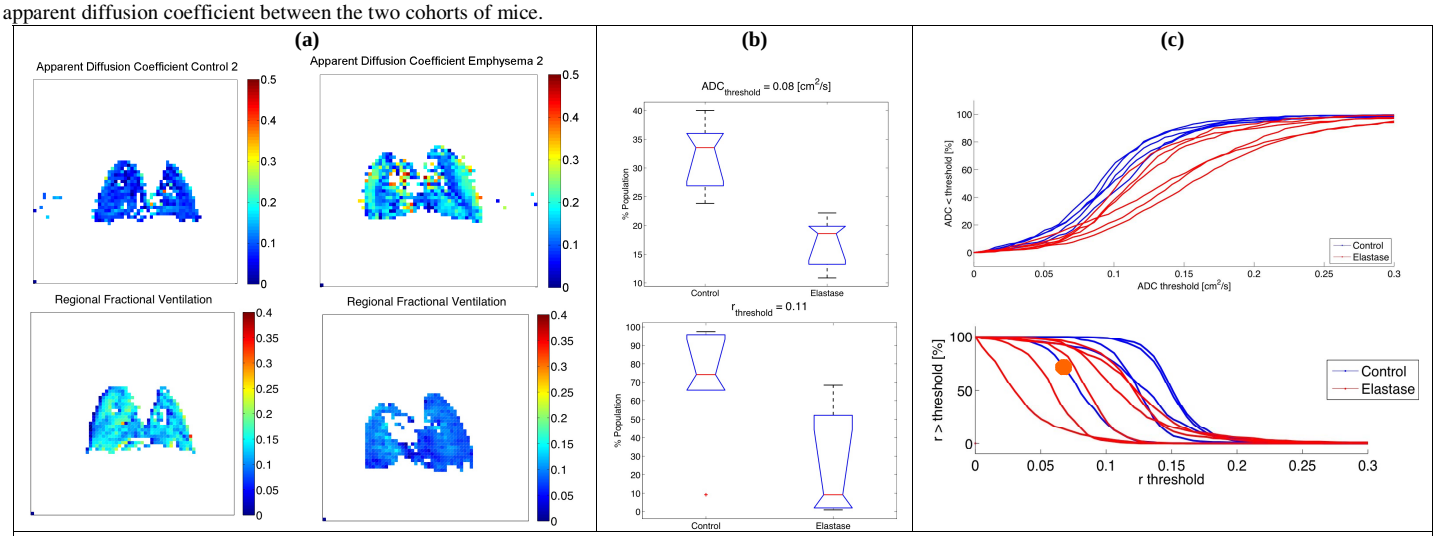

Figure 1. (a) Representative maps of fractional ventilation; **(b)** Comparison between percent population of voxels falling above or below the shown r and ADC cutoff values respectively; **(c)** Variation of voxel population falling above the r cutoff and below the ADC cutoff values.

RESULTS AND DISCUSSION: Maps of fractional ventilation and ^{3}He ADC were calculated for each animal. Figure 1.a shows representative r and ADC maps for one mouse from each cohort, namely C2 and E2. Qualitative comparison of these two animals shows that ADC distribution is more uniform with a lower value in the healthy mouse compared to the elastase one. Fractional ventilation on the other hand shows a higher average value, again with a more uniform distribution. The mean r value for healthy mice was calculated as 0.13±0.03 versus 0.09±0.03 for elastase-treated mice. This difference is not statistically significant (p = 0.11). The difference between mean ADC values of the healthy and elastase-treated mice on the other hand, 0.10±0.005 cm^2/s and 0.14±0.02 cm^2/s respectively, were significantly different (p = 0.003). It is interesting to note that ADC values in healthy mice show a much tighter distribution compared to elastase-treated animals, whereas standard deviation of r in both groups is comparable.

Observing the distribution histograms of r and ADC in all mice (not shown), shows that distributions in healthy animals are mostly symmetric with a relatively similar width. Distributions in some elastase-treated mice however are distorted in several ways (either substantially widened, skewed, or asymmetric). Therefore we attempted to compare the area under the histograms using a certain cutoff value, to also include information about the heterogeneity of distribution of these parameters. The $r_{threshold}$ was varied between 0.0 and 0.3 and the percentage population of voxels that assume $r > r_{threshold}$ were calculated in each mouse lung (Figure 1.c). In general, healthy lung voxels stay above the threshed longer than the elastase-treated ones. The healthy animal marked with the X in Figure 1.c appears to be an outlier because of substantial overlap with elastase-treated mice. In a similar fashion, for ADC maps, the $ADC_{threshold}$ value was varied between 0.0 and 0.3 cm^2/s and the percentage population of voxels that assume ADC<$ADC_{threshold}$ were calculated in each mouse lung (also in Figure 1.c). Finally using arbitrary cutoff values as $r_{threshold}$ = 0.11 and $ADC_{threshold}$ = 0.08 cm^2/s the percent population of voxels in each lung that fall either above or below each cutoff value respectively, were calculated and shown in Figure 1.b (outliers are considered the datapoints with values beyond the ends of the whiskers. For fractional ventilation the mean population of voxels above the cutoff value in healthy lungs was 69% versus 26% in elastase-treated mice. This difference is statistically significant (p < 0.05). As can be seen the one healthy subject discussed before is judged as an outlier based on the criteria laid down earlier. For ADC distribution the mean population of voxels below the cutoff value in healthy lungs was 32% versus 17% in elastase-treated mice. This difference is statistically significant (p = 0.001).

CONCLUSION: Preliminary results show that regional measurements of fractional ventilation and ^{3}He ADC are sensitive metrics to elastase-induced changes in mouse lungs. It was found that lumping the entire distribution of the measured parameters into a mean value may not be a suitable metric in differentiating between the healthy and diseased lungs, possibly as a result of an inherently diminished sensitivity. Grouping the abnormal voxels together can enhance the sensitivity of the measurements in detecting structural and functional changes in the lung. This fact was demonstrated using a simple thresholding method, using arbitrary cutoff values for r and ADC. In both cases the significance of the difference between healthy and elastase-treated mice were improved.

REFERENCES: [1] Deninger AJ, *et al.* Magn. Reson. Med. 48 (2002), 223-232.