

Quantitative Prediction of Lung Disease with Hyperpolarized Gas MRI – Validation in a Murine Model of Emphysema

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INTRODUCTION: Chronic obstructive pulmonary disease is a morbid disease with a high mortality rate; it is among the 4 leading causes of death in the US. Non-invasive methods capable of visualizing structural and functional changes in the lung have great potential for assisting the diagnosis and therapeutic monitoring of this and other pulmonary diseases. Hyperpolarized (HP) ³He MRI, a non-invasive imaging technique, has demonstrated sensitivity to airway remodeling. In this work, we assess the sensitivity of two HP ³He MRI-based measurements, gas diffusivity (a measure of lung structure) and ventilation (a measure of lung function), to detect elastase-induced changes in a murine model of emphysema. Our central hypothesis is that combining a measure of lung function and structure will be the most effective strategy for detecting emphysematous changes in the lung.

METHODS: A randomized prospective study was performed in order to show that a combination of structural and functional pulmonary measurements is better at classifying emphysema than structural or functional metrics alone. 12 male BALB/c mice (3~4 month old; 26±2 g body weight) were randomized into two cohorts: 1) healthy controls (6 animals) and 2) elastase-induced emphysema (6 animals). The emphysema model was induced as described in [1], and the level of emphysema induction was confirmed histopathologically. The animals were sedated with 100 mg/kg IP ketamine and 10 mg/kg xylazine, and then tracheotomized with a 1.5-mm endotracheal tube prior to imaging. Blood oxygenation, heart rate, and temperature were continuously monitored during the study. The mice were mechanically ventilated using a computer controlled MRI compatible ventilator (ventilation parameters: V_T, 1.2 ml/100 g body weight; 110 BPM; I:E=1:2; FIO₂, 20%). During HP lung imaging the animals were switched to 4:1 ³He:O₂ with identical ventilation parameters. Imaging was performed on a 50-cm 4.7-T MRI scanner (Varian, Inc.) equipped with 12-cm, 25-G/cm gradients. The mice were placed supine in the magnet, and a surface coil (1" diameter, 152.95 MHz) with adjustable orientation was placed on top of the chest. For the ventilation measurements, multi-slice images were acquired using a fast gradient echo pulse sequence with the following parameters: FOV=3 cm × 3 cm, THK=4 mm, α=20° (r) and 45° (ADC), MS=64 × 64 pixels (planar resolution of ~470 μm). Fractional ventilation was measured as described earlier in [2]. ADC images were obtained using a DW-GEMS imaging pulse sequence with Δ = 1 ms, and b-values = 0.0 and 2.18 s/cm² along the phase encoding direction. Pulse width calibration was performed on the loaded RF coil to estimate the applied flip angle for each animal. Following imaging, each animal was euthanized, their lungs harvested and fixed in formalin at 20 cm H₂O. Lung histomorphologic analysis was performed on the section of lung corresponding to the imaged slices. Image analysis was performed in MATLAB (MathWorks) using custom programs. Statistical analysis was performed using STATA 10 (StataCorp).

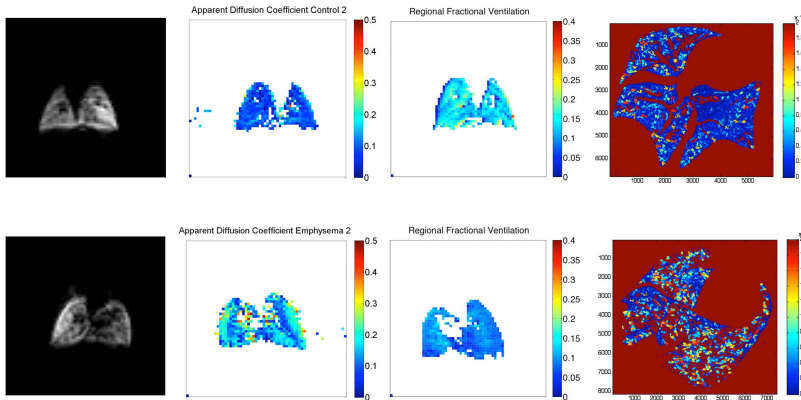


Figure 1. Top and bottom rows show characteristic control and emphysematous mouse results, respectively. Columns from left to right depict ³He image, ADC and r maps, and a plot of surface area based on individual alveoli size (morphologic data).

	<ADC (cm ² /s)>	<r>	<L _m (m)>
Controls	0.102 [0.099-0.104]	0.13 [0.127-0.132]	0.55 [0.52-0.57]
Emphysema	0.133 [0.130-0.136]	0.084 [0.082-0.086]	0.74 [0.58-0.90]

Table 1. Mean values and 95% confidence intervals.

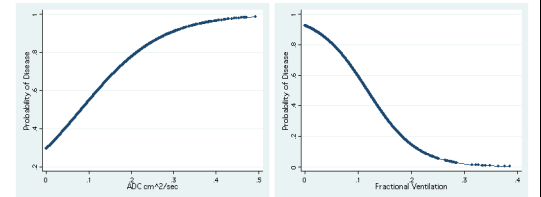


Figure 2. Left curve: probability of disease as a function of ADC value alone. Right curve: probability of disease as a function of fractional ventilation alone.

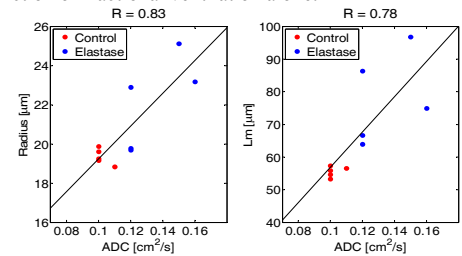


Figure 3. Left curve: Correlations between mean alveoli radius and ADC. Right curve: n alone. Correlations between L_m and ADC.

RESULTS AND DISCUSSION: Maps of fractional ventilation (r) and ³He ADC were calculated for each animal. Figure 1 shows representative helium images, r and ADC maps, and plots of linear mean intercepts for a representative control and emphysema mouse. These images demonstrate that the emphysematous lungs are slightly larger in size than their normal counterparts and possess a more heterogeneous filling pattern. The mean ADC, <ADC>, is larger and the mean fractional ventilation, <r>, is smaller in the emphysematous group. This observation is statistically significant (2-group Hotelling's T² means are different at < 0.001%; individual unpaired t-tests are significant at < 0.001%). This is caused by tissue destruction that increases the mobility of ³He gas in the lungs and decreases regional ventilation. Mean and 95% confidence intervals are shown in Table 1. As expected, the average linear mean intercept, <L_m>, is larger in the emphysema group (unpaired t-test significant at 1% level), thus confirming the model. We note in passing that <L_m> and <ADC> for individual subjects correlate well (ρ_{ADC,L_m} = 0.59). Logistic regression was used to study whether ADC and r alone or in combination can be used to classify pixels from the control and emphysematous groups. These regression models were used to develop a prediction model to determine if a segment of lung comes from a diseased animal. Figure 2 shows the probability of having emphysema based on measures of ADC and r alone. These curves suggest that regions of the lung with low ADC or high fractional ventilation are likely to come from normal subjects, while regions of the lung with high ADC or low r come from diseased subjects. This analysis unexpectedly shows that fractional ventilation alone is better at classifying disease than ADC alone (70.5% of pixels correctly classified using r alone as opposed to 62.9% based on ADC alone). Using both ADC and r increases classification accuracy to 74.8%. These results give the following model for calculating the probability that the region of the lung comes from an emphysematous animal: Pr(Disease) = exp(2.24+7.84×ADC-24.7×r)/(1+exp(2.24+7.84×ADC-24.7×r)). This represents the central finding of this abstract and suggests that anatomic and functional measures in combination are best at determining whether a region of lung comes from a diseased or normal animal. Figure 3 shows the correlations between the histological indices (mean alveoli radius and L_m) and ADC values.

CONCLUSION: Preliminary results show that regional measurements of fractional ventilation, a measure of lung function, and ³He ADC, a measure of lung morphology, are sensitive to elastase-induced changes in mouse lungs. Both measures are capable of differentiating diseased and normal animals, and combining both measures is the most effective strategy for determining if a region of the lung originated from a diseased animal. Regression models provide the means to calculate the probability on which to base the differentiation.

REFERENCES: [1] Emami et al., J. Appl. Physiol. 104 (2008), 773-86. [2] Deninger AJ, et al. Magn. Reson. Med. 48 (2002), 223-232.