Quantitative Assessment of Chronic Exposure to Cigarette Smoke in Mouse Lungs by Hyperpolarized Gas MRI


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INTRODUCTION: Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the United States and is projected to become the third leading cause of death worldwide by the year 2020. While several factors contribute to the development of COPD, such as occupational exposure and air pollution, tobacco smoking is the major contributing factor to the development and progression of this group of respiratory diseases. Hyperpolarized (HP) $^3$He diffusion MRI as a non-invasive imaging technique has demonstrated sensitivity to airway and acinar remodeling. In this study, we utilized a murine model of chronic exposure to cigarette smoke to acquire both apparent diffusion coefficient (ADC) and ventilation of HP $^3$He in the mouse lungs. The goal of this work was to assess the sensitivity of these HP gas MRI techniques to cigarette smoke-induced changes in lung function and structure as a method of early and effective diagnosis of COPD.

METHODS: Male BALB/c mice (3–4 month old, 26 ± 2g) were randomized into three 10-animal cohorts: 1) naïve, 2) control (housed in a sealed box ventilated with forced room air), and 3) smoked (housed in an identical sealed box ventilated with forced smoked air for 6 months). Prior to imaging, animals were anesthetized, intubated with a 1.5-mm endotracheal tube and mechanically ventilated using a custom small-animal MR-compatible ventilator with a delivery accuracy of ±100 mL/breath. Blood oxygenation, heart rate, and temperature were continuously monitored.

RESULTS AND DISCUSSION: Figure 1 shows representative maps of fractional ventilation and ADC, along with the corresponding frequency distribution histograms for one animal from each group. Ventilation measurements were statistically similar among the three cohorts, suggesting that the smoke exposure caused minimal modification of airway lumen. The ADC measurements however demonstrated that the smoked lungs’ microstructures were somewhat larger and more heterogeneous than those of the other groups. Table 1 summarizes the experimental results as whole-lung mean ADC values with standard error of the mean in each group. Threshold analysis allows for better stratification of localized disease foci; the optimal ADC threshold includes ~91% of the ADC distribution in the smoked group, but ~97% in their control naïve counterparts. Figure 2 shows the pairwise analysis of variance for group mean ventilation and ADC values in all three cohorts, and the corresponding p-values. The difference in ventilation between the healthy (naïve and control) mice and smoked mice was statistically insignificant, whereas a significant difference in ADC between healthy and smoked mice was observed.

CONCLUSION: Preliminary results show that regional measurements of $^3$He ADC, a measure of lung morphology, is sensitive to differences between smoke-exposed mice over a period of 6 months and the healthy controls. Measurements of ventilation are unaffected over this time period, suggesting that this murine model of chronic exposure to cigarette smoke primarily resembles emphysematous changes in human lungs, as opposed to chronic bronchitis disease. $^3$He ADC is a promising tool for the study of this model and the asymptomatic changes resembling characteristics of the early human disease.