Imaging Structural Changes in Mice Lungs After Long-term Exposure to Cigarette Smoke

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INTRODUCTION: Chronic obstructive pulmonary disease (COPD) is a major health concern to the international community, affecting millions and showing an ever increasing mortality rate. Contributing factors to the development of the disease include occupational exposure and air pollution; the most significant, however, is tobacco smoking. Hyperpolarized (HP) gas MRI has proven to be a safe and non-invasive way to elucidate sensitive pulmonary changes including airway and acinar remodeling. This study applies HP 3He MRI to a murine model of chronic exposure to cigarette smoke to examine changes in apparent diffusion coefficient of helium diffusivity in the airways. The mouse smoke-exposure model is a well-established and valuable model for the study of human pulmonary response to chronic cigarette smoke. In this way, we aim at monitoring cigarette smoke-induced changes in lung function and structure that may have monitoring or diagnostic value in assessment of COPD.

METHODS: Female C57BL/6 mice (3–4 month old; 22±2g) were randomized into two 10-animal cohorts: mice received nose-only exposure to either 4% smoke from 3R4F cigarettes, or air only (controls), for 2 hr/day, 5 days/week for 18 months. 5 mice in smoke-exposed and 8 in control group survived the entire duration of the study due to the exposure time close to their lifetime. The mice received a normoxic mixture of 3He:O2 (4:1), tidal volume = 1 ml/100g body weight; 110 BPM; I:E=1:2; FIO=20%. The animals’ peak inspiratory pressure (PIP) was continuously monitored and recorded by a high-precision MR-compatible optical pressure transducer (Samba Sensors AB). Before starting the imaging, mice underwent an alveolar recruitment maneuver using a stepwise sequence of positive end-expiratory pressure (PEEP) to minimize the effect of initial atelectasis on ADC measurements [1]. Imaging was performed with a centric phase-encoding gradient echo imaging pulse sequence in a 50-cm bore 4.7-T MRI scanner (Varian, Inc.) equipped with a 12-cm, 25-G/cm gradients and a 1-1/2″-ID quadrature 8-leg birdcage body coil (Stark Contrast). Coronal slices were acquired with an interleaved diffusion-weighted imaging pulse sequence using the following imaging parameters: FOV=3×3cm², ST=5mm, MS=64x64, α=4–5°, TR/TE=6.6/4ms. For ADC imaging, the lung inflation level was controlled by varying the inhalation time at a fixed inspiratory flow rate, corresponding to PIP levels ranging from 3 to 30 cmH2O (Figure 1). Mice were ventilated with five to eight identical breaths of HP He:O2 (4:1) at the designated inflation level followed by a 3-sec breath-hold during which five diffusion-weighted images were acquired corresponding to b-values = 0.00, 3.73, 2.18, 1.00 and 0.00 s/cm². Diffusion sensitizing gradient was applied along the phase-encoding (L-R) direction with the following timing parameters: Δ=1ms, δ=200µs, and τ=189µs.

RESULTS AND DISCUSSION: Figure 1 shows HP 3He spin density and corresponding ADC maps of a representative mouse lung as a function of increasing inflation volume. A qualitative correlation between PIP and ADC was observable in all animals. Figure 2 illustrates how ADC varied as a function of PIP among smoked and control mice. Among all subjects, ADC increased with inflation pressure and reached a plateau around PIP = 15 cmH2O. Three trends readily distinguish smokers: higher ADC values at starting low PIP level, higher ADC values at peak PIP level, and a larger growth rate. The higher ADC values found in smokers are readily explained by pulmonary structural differences, including increased alveolar size, while the faster growth rate results from an elevated compliance. Figure 3 shows representative histology results from an 18-mo and a 6-mo smoked animal. Qualitative examination of the slides shows how alveolar size increases with the duration of smoking. The 6-mo smoked mice results were presented and discussed earlier [2], and included here for comparison. Figure 4 summarizes ADC results comparing smoked and control mice, including mean values and growth rate as a function of pulmonary pressure. 18-mo smoked mice show higher ADC values compared to 18-mo controls (0.149 vs. 0.135 cm²/s), reflecting larger alveolar size, as well as a higher normalized growth rate (0.25 and 0.22), reflecting larger static compliance. At six months, mean ADC values for control and smoked mice were 0.111 and 0.121 cm²/s, respectively.

CONCLUSION: Comparison of ADC results has proven to provide a useful marker for tracking underlying remodeling of lung tissue resulting from smoking. Structural changes, specifically larger alveolar size, can be observed through higher ADC values in smoked mice compared to controls. Additionally, the rate of change of ADC as a function of PIP is higher in smoked mice, which corresponds to an increased pulmonary compliance. Such results highlight the potential role for these methods in the non-invasive in vivo diagnosis and monitoring progression of smoke-exposed changes in the lung.