Imaging of Airway Remodeling in a Murine Model of Bronchial Hyper-responsiveness Using Hyperpolarized Gas MRI

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INTRODUCTION: Current asthma diagnosis is predominantly based on pulmonary function tests and clinical symptoms. Often, manifestations of clinical symptoms are detected in later stages of disease progression; therefore the development of a sensitive tool for early detection of this disease is of great significance. Hyperpolarized (HP) gas MRI provides a non-invasive tool for direct imaging of gas flow and distribution in the airways with high sensitivity to localized and early-stage alterations in airway remodeling and narrowing. It also provides a gas diffusivity measure in the airways shown to be strongly related to airway size and geometry. Regional and co-registered measurements of apparent diffusion coefficient (ADC) of ^{3}He and regional pulmonary ventilation (r) can help evaluate simultaneous changes in lung structure and function. In this study we tested the hypothesis that acute asthmatic changes in a murine model of allergic airway inflammation can be reliably measured with quantitative gas ventilation and diffusion MRI.

METHODS: Three groups of BALB/c mice were studied in a model of allergic airway sensitization: (1) naive (n=6), (2) sensitized control (n=6) and (3) sensitized/allergen challenged (n=9). Mice receiving Aspergillus fumigatus exposure were sensitized with an IP injection on the first and seventh day of the study, and received a nasal instillation on the fourteenth day. The mice were sedated with 100 mg/kg IP ketamine and 10 mg/kg xylazine, and subsequently tracheotomized with a 1.5-mm ET tube. Heart rate, blood oxygenation, and temperature were continuously monitored throughout the imaging session. The mice were connected to a custom-designed small animal ventilator equipped with real-time monitoring of peak inspiration pressure (PIP) and capable of delivering the breathing gas with an accuracy of ±100µL/breath. Mice were ventilated with a mixture of ^{4}He:O_2 (4:1) at 110 BPM with I:E=1:2 at a V_T=0.15TLC as measured with a rodent plethysmography system. For imaging ventilation switched to ^{3}He:O_2 (4:1). Imaging was performed on a 50-cm 4.7-T MRI scanner (Varian, Inc.) equipped with 12-cm, 25-G/cm gradients and quadrature 8-leg birdcage body coil. Three-slice images were acquired using a fast gradient echo imaging pulse sequence with: FOV=3×3cm^2, THK=5mm, α=15° (r) and 20° (ADC), MS=64×64 pixels (planar resolution of ~470 µm). Fractional ventilation was measured as described in [1]. ADC images were obtained using a diffusion-weighted imaging pulse sequence with Δ=1ms, and b-values = 0.0, 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. Each animal was euthanized after imaging, their lungs were harvested and fixed in 10% formalin under 20 cmH_2O and lung histology slides were collected.

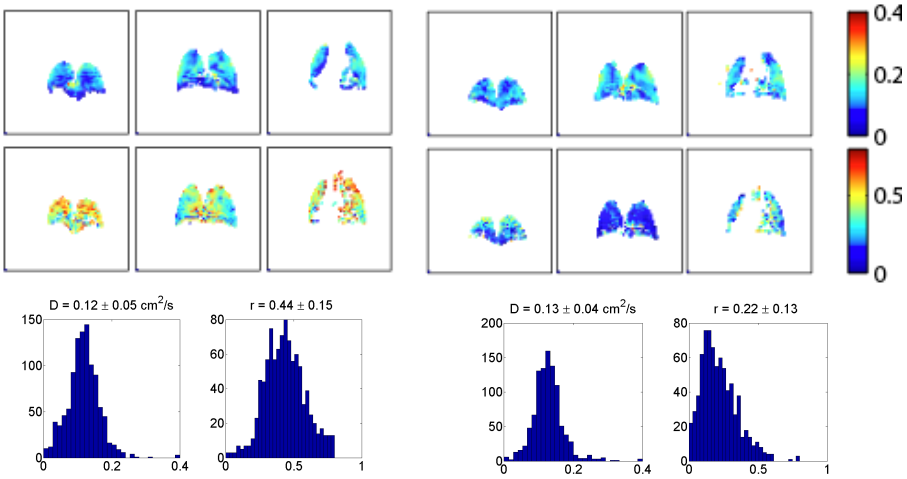

Figure 1. Representative ADC (top row) and r (middle row) maps from naïve (columns 1-3) and asthma (columns 4-6) cohorts. Posterior (columns 1, 4), middle (columns 2, 5) and anterior (columns 3, 6) slices are shown in rows 1 and 2, followed by corresponding frequency distribution histograms in row 3 (naïve ADC and r, asthma ADC and r).

RESULTS: Representative maps of ADC and r, and their corresponding frequency distribution histograms are shown in **Fig. 1** for naïve and asthmatic cohorts. A summary of group r and ADC distributions are shown in **Fig. 2**. Results indicate that the asthmatic lungs have a statistically similar ADC values (0.13± 0.01 cm^2/s for both naïve and asthmatic mice, p-value=0.7767) but lower mean r values across the two cohorts (r=0.38±0.04 for native vs. r=0.33±0.07 for asthmatic cohort, p-value=0.0224). This suggests that alveolar remodeling is not a significant factor in acute asthmatic response, whereas a significant small airway remodeling is manifested. **Fig. 3** shows the relationship between PFT metrics and ventilation across cohorts. A significant decline in dynamic compliance (Cdyn) was observed after model induction in correlation with r (p-value=0.05 across the naïve and asthmatic cohorts). The decline in r between naïve and asthmatic cohorts (p-value=0.02) suggests that ventilation MRI provides a greater sensitivity to asthma-induced changes in airways structure. No significant difference in airway resistance (RI) however was observed among the different groups (p-value=0.61 between asthmatic and naïve cohorts), which suggests that the decline in ventilation efficiency is driven not only by airway narrowing, but also by the loss of wall recoil.

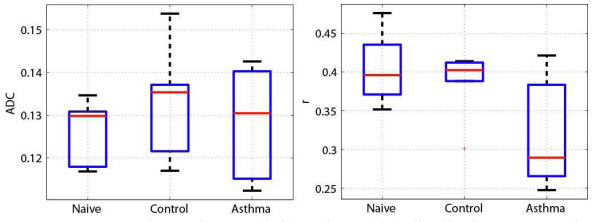

Figure 2. Comparison of ADC (left) and r (right) distributions among the groups (naïve, control, asthma).

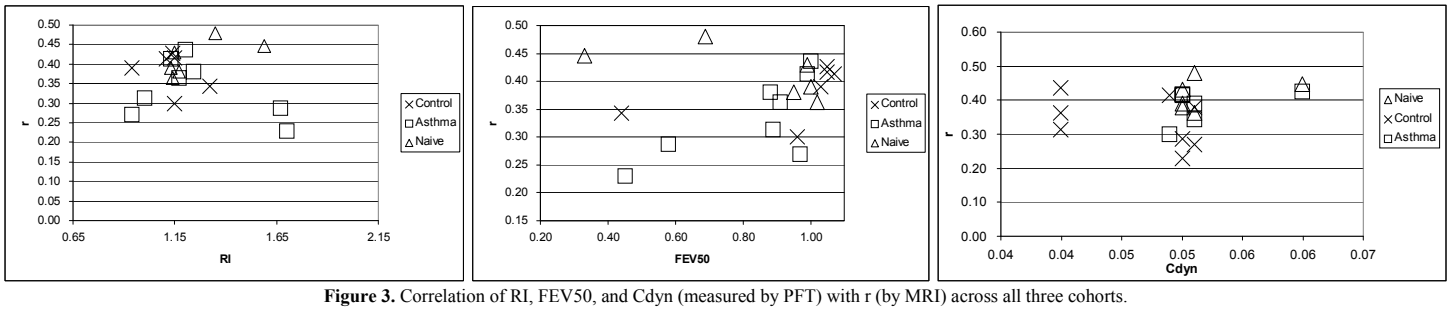

Figure 3. Correlation of RI, FEV50, and Cdyn (measured by PFT) with r (by MRI) across all three cohorts.

CONCLUSION: While altered alveolar function does not appear to have a considerable role in the acute asthmatic response in this murine model of asthma (as evidenced by insignificant change in ADC values), a significant small airway remodeling is manifested in decreased ventilation efficiency, also supported by a significant decline in overall dynamic compliance. Preliminary results suggest that the HP gas MRI of regional fractional ventilation can serve as a more sensitive metric to detect and quantify formation and progression of asthmatic changes in the lung, compared to more traditional pulmonary function tests.

REFERENCE: [1] Emami K, *et al.*, Magn Reson Med. 2010 Jan; 63(1):137-50.