Imaging Regional Alterations of Gas Exchange in a Murine Model of Emphysema

P. Mongkolwisetwara1, K. Emami1, H. Hamedani1, H. Profska2, Y. Xin1, Y. Xu1, N. N. Kuzma1, S. J. Kadlec1, M. Ishii3, and R. R. Rizi1

1Radiology, University of Pennsylvania, Philadelphia, PA, United States 2Otolaryngology–Head & Neck Surgery, Johns Hopkins University, Baltimore, MD, United States

INTRODUCTION: Pulmonary imaging with hyperpolarized (HP) 3He MRI is a sensitive probe for lung microstructure and function. Emphysema, a primary subcategory of COPD, is characterized by abnormal enlargement of lung components from the distal to the terminal bronchioles. It is accompanied by alveolar wall destruction and tissue density loss. In this work, we use HP 3He MRI measurements of alveolar partial pressure of oxygen (P O2), apparent diffusion coefficient (ADC), and fractional ventilation (r) in conjunction with localized histological analysis to assess the changes in lung function and structure in an elastase-induced murine model of emphysema. Measurements of P O2 and r are directly related to alveolar gas exchange and gas replacement respectively, and can further our basic understanding of the underlying mechanisms of emphysema onset and progression.

METHODS: A group of male BALB/c mice (n=6) were divided into two equal-numbered cohorts: (1) healthy controls (2) elastase-induced. Emphysema was induced through a single intratracheal instillation of 22U/100g of porcine pancreatic elastase with 12-cm 25G/cm gradients. Animals were sedated with 100mg/kg intraperitoneal ketamine and 10 mg/kg xylazine. Treacheotomy was performed with a 1.5-mm ET tube. Saturation level of blood oxygen and heart rate were monitored using an MR-compatible rodent pulseoximeter (Nonin Medical, Inc., Plymouth, MN). Mice were mechanically ventilated with a tidal volume of 1.2ml/100g body weight at 110 BPM and I:E=1:2 with breathing air. During imaging, the ventilation was switched from air to a mixture of 3He:O2 (4:1) with identical ventilation parameters. Imaging was performed on a 50-cm 4.7-T MRI scanner equipped with 12-cm 25G/cm gradients. The mice were placed supine in the magnet and a 1″-diameter surface coil tuned to 152.95 MHz was placed on top of the chest, while the animal was positioned supine in the magnet. For the ventilation and P O2 measurements, multi-slice coronal images were acquired using a fast gradient echo pulse sequence with FOV=3x3cm2, matrix size=64x64 pixels (planar resolution of ~470 μm). Fractional ventilation r, ADC, and P O2 were imaged as described earlier [1, 2]. ADC images were obtained using a diffusion-weighted gradient echo 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 sequence. The mice were placed supine in the magnet. For the

RESULTS: Figure 1 shows representative maps of P O2 in control and emphysematous animals. Figure 2 shows P O2 mean and standard deviation for the two groups showing that the healthy group has a smaller P O2 value of 94.37±19.44 mbar compared to the elastase group at 126.99±13.19 mbar (the difference is not quite statistically significant with p = 0.074, which is most likely a result of the small sample size in this study and will be addressed as the study progresses), but it shows the difference on a scale of the average values of the two groups. Figure 3 shows the correlation between P O2 and ADC, as well as fractional ventilation. It can be seen that the P O2 measurements can differentiate animals that appear the same under both ADC and ventilation metrics. Although the mean ADC of elastase-induced mice is higher than that of healthy animals, P O2 shows a compromised O2 uptake through the alveolar membrane, most likely due to destruction of alveolar walls and loss of elastic recoil. Figure 4 shows the correlations between the histological indices (mean alveoli radius and Lm) and ADC values indicating effective elastase model induction.

CONCLUSION: Our preliminary results show a non-negligible change in alveolar partial pressure of oxygen between controlled and elastase-induced mice, indicating that P O2 imaging by HP 3He MRI can be a sensitive tool to investigate lung disease models, specifically those affecting the membrane function. The higher value of the mean linear intercept and ADC represent tissue destruction in the elastase-induced animal, which are concurrent with the compromised O2 uptake efficiency in these animals as evidenced by an elevated P O2 and a declined fractional ventilation measurements.