High Resolution Measurement of Regional Alveolar Partial Pressure of Oxygen in the Mouse Lung by Hyperpolarized 3He MRI

K. Emami[1], J. M. Woodburn[1], R. A. Guyer[1], S. Pickup[1], S. Kadlecek[1], M. Ishii[1,2], R. V. Cadman[1], J. Yu[1], H. H. Kim[3], M. Stephen[4], W. B. Gefter[1], and R. R. Rizi[1]

[1]Department of Radiology, University of Pennsylvania, Philadelphia, PA, United States, [2]Department of Otolaryngology, Johns Hopkins University, Baltimore, MD, United States, [3]Department of Chemistry, University of Pennsylvania, Philadelphia, PA, United States, [4]Department of Pulmonary, Allergy, and Critical Care Division, University of Pennsylvania, Philadelphia, PA, United States

INTRODUCTION: Non-invasive, regional assessment of lung function has the potential to markedly enhance the monitoring of progression of pulmonary diseases, as well as quantitative assessment of response to therapeutic intervention. Over the last decade, quantitative Hyperpolarized (HP) ^{3}He MRI techniques have been developed to address crucial aspects of both lung structure and function. Alveolar partial pressure of oxygen is one of the important pulmonary markers with high sensitivity to alterations of regional lung physiology. The characteristic depolarization of HP ^{3}He in presence of oxygen has been utilized by many researchers in quantitative measurement of alveolar oxygen tension. With the exception of a few recent works, the majority of currently existing P_AO_2 measurement techniques are tailored towards large animals and humans, and are not directly implementable on rodents. These techniques rely on acquiring a series of images during a relatively long breath-hold followed by inhaling HP ^{3}He breaths [1]. The signal decay history is then fit to a model of helium-oxygen interaction to yield P_AO_2. This approach is impractical in mice, due to – among other factors – higher respiratory rate, higher oxygen uptake rate, and inability to tolerate the necessary long breath-hold. the characteristic time scale of O_2-induced depolarization (16 sec at physiological O_2 tension) is incompatible with several aspects of the mice physiology and the maximum tolerable breath hold (~5 sec, if undesirable physiological responses are to be avoided) does not allow adequate depolarization to accurately measure the O_2 tension. Additionally, the faster oxygen uptake rate produces a measurement environment in which gas redistribution during the initial 1~2 sec of the breath hold is not easily separated from O_2-induced depolarization. Finally, the small lung size causes regional information to be washed out by gas diffusion unless special care is taken to keep delays between images short. The errors associated with gas diffusion in large-animal P_AO_2 measurements are commonly avoided by limiting regional measurements to relatively large-size bins. This approach leads to unacceptable loss of regional information in smaller animals. However, the small animals present a compensatory opportunity for signal-averaging because of the small amount of gas used per breath and great controllability on the ventilation patterns achievable by programmable small animal ventilators. Ability to perform these measurements with high accuracy in mice, apart from availability of numerous interesting disease models, enables us to tailor ventilation parameters under full control and repeat measurements with an unprecedented reproducibility level that is difficult or impossible in larger species.

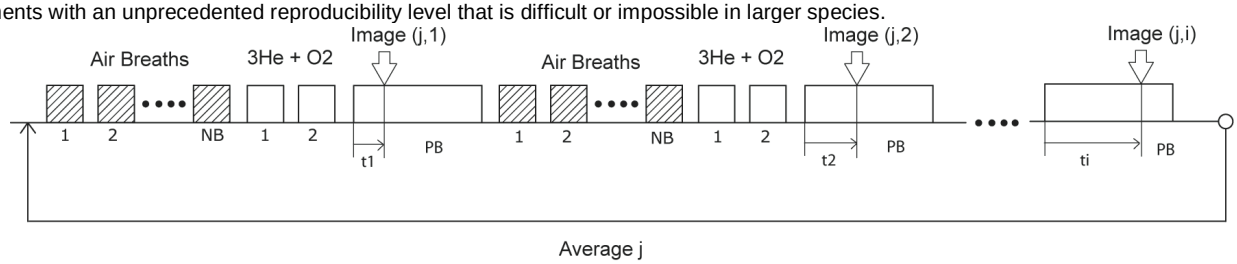

Figure 1. Ventilation-imaging scheme for measurement of regional P_AO_2 in mice lungs using multiple averages and time points.

METHODS: The details of this measurement technique are described in [2]. The basic idea is to capture the time points of ^{3}He signal decay across multiple different breath holds (Figure 1). This approach eliminates the dependency of acquired images within the same breath hold, and therefore only the helium-oxygen interaction effects will be elucidated in the signal history. The animal is ventilated with enough number of air breaths (50 in this experiment breaths) between each imaging step to washout any residual ^{3}He in the lung and guarantee the same initial conditions for each acquisition. After this step mouse is then provided with 10 breaths of ^{3}He:O_2 (4:1) mixture. A short breath hold then follows during which one image is acquired at a predefined delay time (t_i) from the beginning of the breath hold, cycling through the following values: 0.5, 4.5, 1.0, 3.5, 1.5 and 2.5 [s]. This time delay allows the initial polarization to decay according to: $S(t)=S_0 \exp(-P_AO_2\, t/\xi)$, where ξ is the decay time constant of ^{3}He in presence of oxygen. Upon completion of one cycle, the whole cycle is repeated for several times. Upon completion of the entire acquisition, images with the same time points are averaged to yield a high SNR. The resulting sequence of images is fit voxel-by-voxel to a model incorporating relaxation due to collisions with O_2. Images were acquired on a 4.7-T small animal MRI scanner and a 12-leg birdcage coil using a fast gradient echo imaging pulse sequence with the following parameters: FOV=3cm, ST=6mm, MS=64×64, flip angle=25°, T_E=2.4ms, and T_R=4.3ms. Typical series of mouse lung images for one cycle are shown in Figure 2.

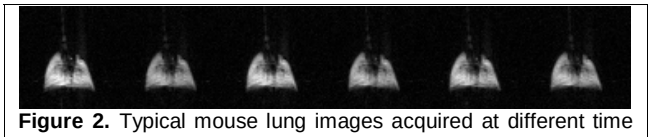

Figure 2. Typical mouse lung images acquired at different time points over separate breath holds. Note the attenuation of signal corresponding to delay times: 0.5, 4.5, 1.0, 3.5, 1.5 and 2.5 [s], respectively.

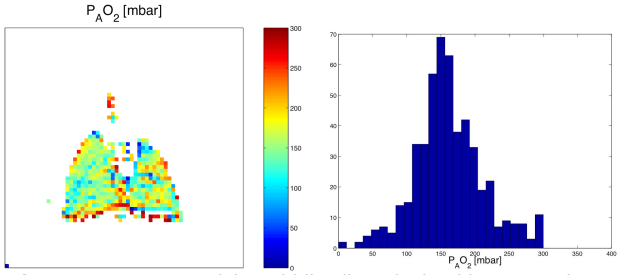

Figure 3. P_AO_2 map of the middle slice of a healthy mouse lung, and the corresponding frequency distribution histogram.

RESULTS AND DISCUSSION: After correcting the entire signal history for the external ^{3}He reservoir depolarization (T1,ext ≈ 45 min), the resulting P_AO_2 map was generated as shown in Figure 3, along with the corresponding frequency distribution histogram. The regional P_AO_2 map has a planar resolution of 470µm. The mean P_AO_2 value of 150 mbar (112 torr) corresponds to normal physiological conditions in rodents and closely meets with overall concentration of the delivered ^{3}He and oxygen mixture. A high value P_AO_2 is observed in the conductive airways as expected. The observed high P_AO_2 values near the diaphragm are believed to be induced by ventilatory motion artifacts. The feasibility of high resolution mapping of regional oxygen tension in mice opens up a wide variety of possibilities in studying transgenic pulmonary disease models in mice and their response to therapeutic interventions.

REFERENCES: [1] Fischer MC, *et al.* Single-acquisition sequence for the measurement of oxygen partial pressure by hyperpolarized gas MRI. *Magn Reson Med*. 2004 Oct;52(4):766-73. **[2]** Emami K, *et al.* A Robust Technique for Measurement of Regional Partial Pressure of Oxygen in Rodents; ISMRM, 16-th Scientific Meeting, Berlin, Germany: 2007.