A Robust Technique for Measurement of Regional Partial Pressure of Oxygen in Rodents

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Introduction: Non-invasive, regional assessment of lung function has the potential to markedly enhance the monitoring of progression of pulmonary diseases, as well as response therapeutic procedures. Over the last decade, quantitative Hyperpolarized (HP) gas 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. Current techniques are, however, mostly tailored towards large animals and humans, and are not easily implemented on small animals, and specifically rodents. These techniques rely on acquiring a series of images during a relatively long breath-hold followed by inhaling HP helium breaths [1]. The signal decay history is then fit to a model of helium-oxygen interaction model to yield partial pressure of oxygen. This approach is impractical in rodents, and is limited by small animals' higher respiratory rate, higher oxygen uptake rate, and inability to tolerate the necessary long breath-hold. the characteristic time scale of O2-induced depolarization (16 seconds at physiological O2 tension) is incompatible with several aspects of the rat physiology. The maximum tolerable breath hold (~5 seconds, if undesirable physiological responses are to be avoided) does not allow adequate depolarization to accurately measure the O2 tension. Additionally, the faster oxygen uptake rate produces a measurement environment in which gas redistribution during the initial 1-2 seconds of the breath hold is not easily separated from O2-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 rodents, 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.

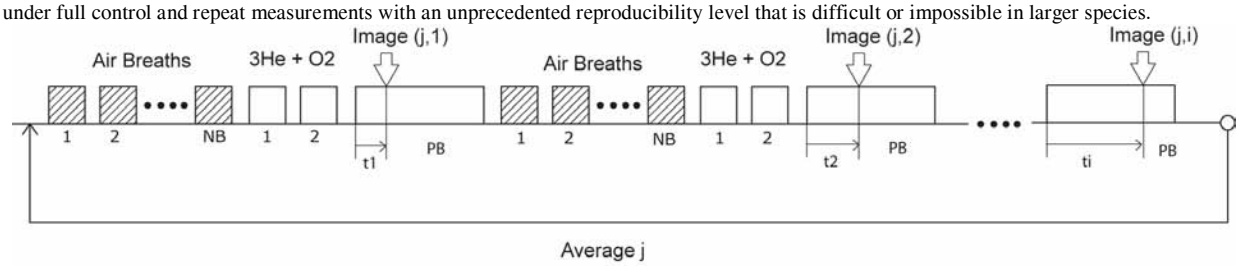
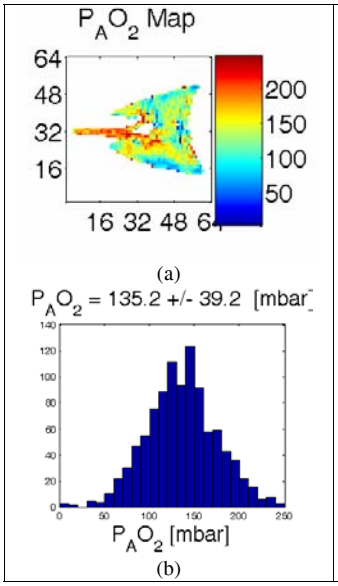
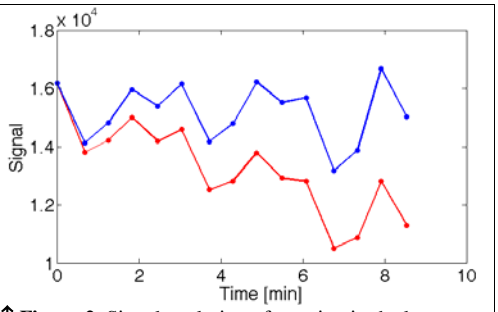


Figure 1. Schematic ventilation sequence diagram of measurement of regional partial pressure of oxygen in rodents using multiple averages and time points.

Methods: The fundamental idea of our proposed technique is to capture the time points of helium 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 (typically 30 breaths) between each imaging step to washout any residual helium in the lung and guarantee the same initial conditions for each acquisition. After this step animal is then provided with a few (2~3) breaths of a known mixture of HP helium on oxygen. The mixture commonly contains the same ratio of ^{3}He:O_2 as that of N_2:O_2 in normal breathing air; i.e. 20.8% O_2. The concentration of the delivered mixture is accurately measured using an oxygen gas analyzer for further verification of results. A short (3~5sec) breath hold then follows during which one image is acquired at a predefined delay time (t_i) from the beginning of the breath hold. 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 hyperpolarization decay time constant of helium in presence of oxygen. A typical imaging sequence makes use of a repeated pattern of delays: 0.5, 4, 1, 2, 1.5, 0.5, 4, etc. Upon completion of one cycle, the whole cycle is repeated for several times (Figure 2). 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. The resulting large signal-to-noise allows accurate determination of P_AO_2 despite the short breath-hold and gas redistribution during the initial period. Images were acquired with a multi-slice gradient echo pulse sequence with FOV=6cm, ST=6mm, RES=64×64 and flip angle=8°.





↑ **Figure 2.** Signal evolution of a region in the lung as a function of time. Notice the repeated 5-point pattern across the three averages. The red curve is the original, and the blue curve is the signal corrected for external polarization effect.

← **Figure 3. (Top)** P_AO_2 map of a middle slice of a healthy rat lung; **(Bottom)** The corresponding frequency distribution histogram.

Results and Discussion: Figure 2 shows a representative signal-time history for an arbitrary voxel in the lung (red line). The overall polarization of helium in the reservoir is constantly decaying with a time constant of T1,ext ≈ 45 mins. The overall signal can be corrected for this external decay effect (blue line), for an improved averaging across multiple breaths. The fit results yield a high resolution map of partial pressure of oxygen. The measured mean P_AO_2 = 135 mbar closely meets with overall concentration of the delivered helium and oxygen mixture. A high value P_AO_2 is observed in the conductive airways. A uniform P_AO_2 gradient can be seen starting at ~150 mbar in the interior regions towards ~80 mbar in the exterior regions.

Conclusion: A novel approach for measurement of partial pressure of oxygen in rodents and small animals is presented. This method is based in averaging multiple time points acquired over several acquisitions. The superior SNR yield reliable high resolution maps of oxygen tension in the lung of rodents. This technique can be further utilized to study various interesting models of pulmonary disease in mice and rats.

Acknowledgements: This work was supported by NIH grants R01-HL64741, R01-HL077241, and P41-RR02305.

Reference: [1] Fischer MC, Spector ZZ, Ishii M, Yu J, Emami K, Itkin M, Rizi R. Single-acquisition sequence for the measurement of oxygen partial pressure by hyperpolarized gas MRI. Magn Reson Med. 2004 Oct;52(4):766-73.