Hyperpolarized Helium Measurements of P_AO_2 Correlate with Neutrophil Inflammation in the Rat Bleomycin Model

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INTRODUCTION: Hyperpolarized (HP) ^{3}He MRI is a technique sensitive to both lung structure (airway size through Apparent Diffusion Coefficient, ADC) and function (alveolar PO_2 and fractional ventilation, r) through direct imaging of respiratory gas molecules. In this work, we investigated correlated changes of these metrics with bronchoalveolar lavage (BAL) measurements and biochemistry in a rat model of interstitial fibrosis secondary to bleomycin.

METHODS: Male Sprague Dawley rats (n=9, 300~350g body weight) were given intra-tracheal bleomycin and 7 (7BR) and 21 (21BR) days after intratracheal bleomycin, they underwent HP ^{3}He MRI to measure r, ADC and P_AO_2. The animals were intubated and connected to a custom-designed small animal ventilator. This ventilator is capable of delivering the breathing gas with an accuracy of ±100µL/breath and real-time monitoring of peak inspiration pressure (PIP). For ventilation imaging, a series of 10 HP gas breaths (^{3}He:O_2, FIO_2=20%) was delivered to the rat at the designated tidal volume V_T = 1.0ml/100g, and one image was acquired after each breath during a 350-ms breath-hold. The HP ^{3}He signal build up in the rat lung was then recursively solved for r to yield the fractional ventilation map, as described earlier [1]. For ADC imaging, rats were ventilated with five identical breaths of HP ^{3}He:O_2 (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/cm^2. This procedure was repeated immediately with identical but reversed polarity diffusion gradient b-values. These 10 diffusion-weighted images were then combined to yield the ADC map of the imaged slice according to a double-acquisition diffusion imaging scheme described earlier [2]. For P_AO_2 imaging, rats inhaled a series of 5 breaths of ^{3}He:O_2 followed by a short 6-sec breath-hold, during which images were acquired at a set of predefined delay times, and the resulting images corresponding to the same slice/delay combination were then averaged and fit to a model of O_2-induced decay and respiratory gas redistribution as described earlier [3]. Images were acquired using a diffusion-weighted gradient echo imaging pulse sequence with centric phase-encoding in a 50-cm bore 4.7-T MRI scanner (Varian Inc) equipped with a 12-cm, 25-G/cm gradients and a 2-3/4"-ID quadrature 8-leg birdcage body coil (Stark Contrast). Images were acquired in the middle coronal slice of the rat lung with the following imaging parameters: FOV=6×6cm^2, ST=6mm, MS=64×64, α=4~5°, TR=6.6ms, and TE=4ms. Diffusion sensitizing gradient was applied along the phase-encoding (L–R) direction with the following timing parameters: Δ=1ms, δ=200μs, and τ=180μs according to the naming convention of [4]. Upon conclusion of imaging, BAL was performed for measurement of white blood cell (WBC) numbers and differential, and BAL protein content as a measure of lung damage. The right lung was fixed for histology and the left lung for measurement of hydroxyproline, a measure of fibrosis. Healthy rats (HR) were similarly tested. Values were expressed as mean ± SD and statistical significance was determined by pairwise t-tests.

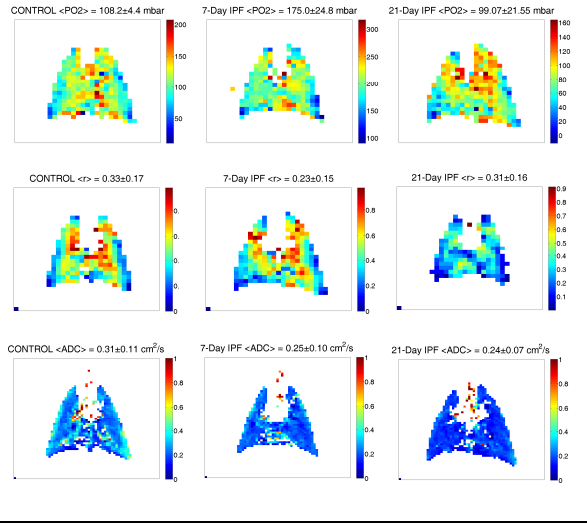

Figure 1. Representative maps of P_AO_2, ADC, and r in HR, 7BR, and 21BR rats.

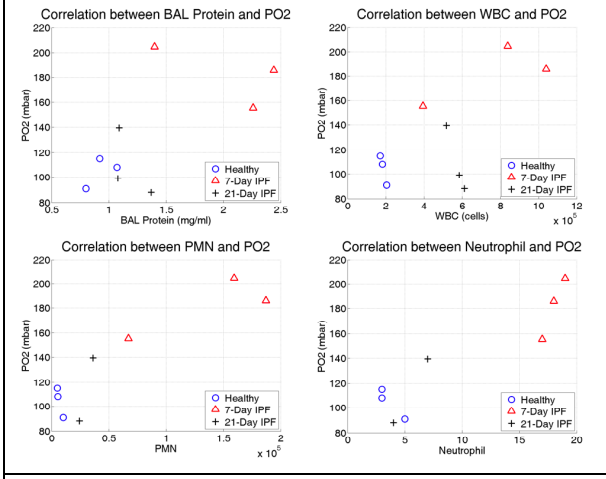

Figure 3. Correlations between P_AO_2 and biological markers.

RESULTS AND DISCUSSION: **Figure 1** shows a representative map of P_AO_2, ADC, and r in HR, 7BR, and 21BR rats. **Figure 2** shows that the overall mean of ADC were not significantly reduced in 7BR (0.25±0.10 cm^2/s) and 21BR (0.24±0.07 cm^2/s) compared to HR (0.31±0.11 cm^2/s). The means of r were also not significantly reduced in 7BR (0.23±0.15) compared to the HR (0.33±0.17) and returned towards normal in 21BR (0.31±0.16). In contrast, **Figure 3** shows the P_AO_2 was significantly ($p < 0.05$) increased in 7BR (175.0±24.8 mbar) compared to HR (108.2±4.4 mbar) and returned toward HR in 21BR (99.07±21.55 mbar). Both the number ($r = 0.868$) and percent ($r = 0.833$) of neutrophils in the BAL fluid was significantly ($p < 0.01$) correlated with the P_AO_2 but there was no significant correlation between BAL cells or protein with ADC or r. Hydroxyproline was unchanged in 7BR but was significantly increased in 21BR (HR = 64.3, 7BR =53.1, 21BR = 95.7 ug/ug lung tissue, $p < 0.05$).

CONCLUSION: In the rat model of pulmonary fibrosis due to bleomycin, P_AO_2 correlated with the extent of neutrophil inflammation in the lung. This suggests that P_AO_2 measured by HP ^{3}He MRI can be a sensitive indicator of pulmonary inflammation and may help with predicting prognosis, and helping with drug development as a non-invasive measure of lung function.

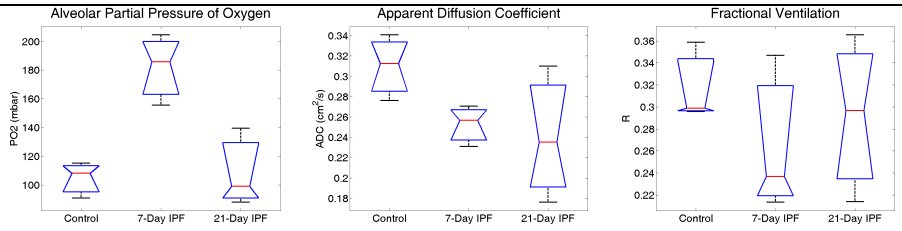

Figure 2. Comparison of group statistics of HP ^{3}He MRI metrics in HR, 7BR, and 21BR rats.

REFERENCES: [1] Emami K, *et al.*, Magn Reson Med. 2010; [2] Emami, K, *et al.* Proc Intl Soc Mag Reson Med 2007; [3] Kadlecek *et al.*, Proc Intl Soc Mag Reson Med 2009; [4] Yu, J, *et al.* J Magn Res Imag 2007.