Comparison of Pulmonary Function Testing with Distribution of Alveolar Oxygen Tension and Apparent Diffusion Coefficient in Asymptomatic Smokers Using Hyperpolarized ^{3}He MRI

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INTRODUCTION: Conventional pulmonary function tests (PFT) provide a global measure over the entire lung as a tool for diagnosis and monitoring of a majority of obstructive and interstitial lung diseases. PFT however is considered to have a poor sensitivity for detecting localized, early or small changes in lung function and structure. The use of hyperpolarized (HP) gas MRI has been under investigation for probing both microstructural and functional aspects of lungs on a regional basis and with potentially higher sensitivity. In this study we compared common PFT measurement with distributions of alveolar partial pressure of oxygen (p_AO_2) and apparent diffusion coefficient (ADC) of ^{3}He obtained with oxygen- and diffusion-weighted HP gas MRI respectively. This comparison was performed in two groups of healthy human subjects and asymptomatic smokers to highlight underlying physiological relationships between the two methods. We also attempted to assess the sensitivity of each group of measurements in differentiating the subject groups and to evaluate the potential of MRI metrics as imaging biomarkers in monitoring active smokers...

METHODS: Ten healthy non-smokers (5 F, 56±8 yrs., BMI=27.3±6.6) and twenty asymptomatic smokers (13 M, 53±12 yrs., BMI=25.3±8.4) participated in p_AO_2 and ADC MRI studies. Before MRI session, PFT was performed on all subjects. p_AO_2 imaging was performed over twelve 13-mm coronal slices with 20% interslice gap, using an interleaved oxygen-weighted gradient echo imaging pulse sequence [Hamedani *et al.* MRM 2011] (spatial resolution 8.3×8.3×15.3mm^3, TR/TE=6.7/3.2ms, FOV=30×40cm^2, α=5°) and ADC imaging was done using an interleaved diffusion-weighted gradient echo sequence with *b*-values=0,1.6 s/cm^2 with similar imaging parameters except for spatial resolution (6.25×6.25×15.3mm^3). A normoxic mixture of ^{3}He:N$_2$:O$_2$ based on 12% Total Lung Capacity was administered at end-expiration in a single breath and images were acquired during a 12-sec end-inspiratory breath-hold. Imaged whole-lung p_AO_2 and ADC mean (μ_{pAO2}, μ_{ADC}), dispersion (σ_{pAO2}, σ_{ADC}) and skewness (γ_{pAO2}, γ_{ADC}) for each subject were compared to PFT results. Pearson's coefficient was calculated for each comparison to relate the global values of PFT with MRI. One-tailed ANNOVA test was performed on both PFT and MRI results for both groups in order to compare the sensitivity of MRI and PFT parameters in differentiating smokers and nonsmokers.

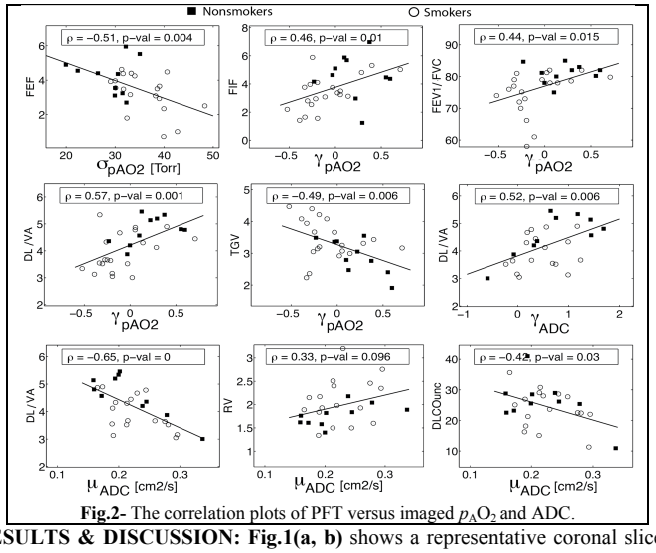

Fig.2- The correlation plots of PFT versus imaged p_AO_2 and ADC.

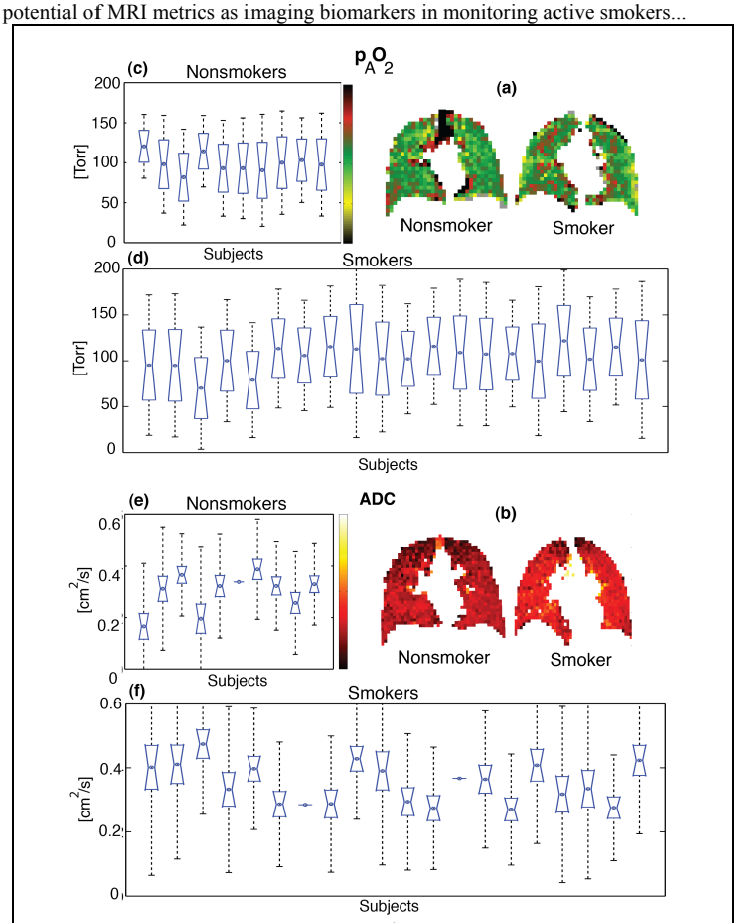

Fig.1- Representative maps of **(a)** p_AO_2 and **(b)** ^{3}He ADC in a healthy subject. Summary of p_AO_2 and ^{3}He ADC measurements in **(c,d)** healthy subjects and **(e,f)** asymptomatic smokers, respectively.

RESULTS & DISCUSSION: Fig.1(a, b) shows a representative coronal slice of p_AO_2 and ADC maps for a representative subject from each group. **Fig.1(c–f)** summarize p_AO_2 and ADC distributions for both groups. The overall p_AO_2 and ADC values for all subjects were in the range of 102.1±11.9 Torr and 0.22±0.04 cm^2/s, respectively. The dispersion of p_AO_2 among all subjects ranged over 33.9±6.1 Torr. No apparent association was observed between ADC and p_AO_2 measurement and their derivatives except for a weak correlation between μ_{ADC} and γ_{pAO2} (r = –0.37, *P* = 0.06). As can be seen from **Fig.1(c,d)**, μ_{pAO2} shows a significant variability among all subjects. The global average p_AO_2 does not show any correlation with any of the PFT metrics either. σ_{pAO2} on the other hand associates with Maximum Forced Expiratory Flow, FEF_{max} (r = –0.51, *P* = 0.004, 95% CI: –0.73, –0.17), suggesting that the heterogeneity of p_AO_2 distribution can be a more sensitive marker to smoking-related changes in the lungs compared to average alveolar oxygen tension. Skewness of the p_AO_2 distribution also shows an interesting trend as it significantly correlates with DL/VA - Diffusion per unit area of Lung Volume (r = –0.57, *P* = 0.001, 95% CI: 0.27, 0.77). γ_{pAO2} also correlated with Thoracic Gas Volume, Forced Inspiratory Flow and FEV_1/FVC as is shown in **Fig.2**. The mean values of ^{3}He ADC (μ_{ADC}) showed a significant correlation with DL/VA (r = –0.65, *P* < 0.001, 95% CI: –0.33, –0.84) and a weaker association with Residual Volume and DLCO. γ_{ADC} also associated with DLCO (r = 0.52, *P* = 0.006, 95% CI: 0.15, 0.71). Finally **Fig. 3** summarized the results of ANNOVA test between the two groups for two key PFT metrics, and p_AO_2 dispersion. Among all measurements performed, σ_{pAO2} (dispersion of oxygen tension in the lungs) had the smallest overlap and most discrimination power between two groups and its *P*-value was significantly less than any other PFT measurements as well as ADC values.

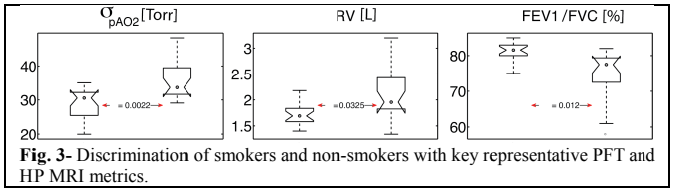

Fig. 3- Discrimination of smokers and non-smokers with key representative PFT and HP MRI metrics.

CONCLUSION: Regional distributions of oxygen tension and diffusivity in lungs show to have significant correlations with key PFT metrics supporting their physiological relevance. However specific MRI metrics, including p_AO_2 dispersion showed an even more discriminatory power compared to gold standards (e.g. FEV_1/FVC). The richer information embedded in regional lung measurements therefore advocates their suitability for further investigation as respiratory biomarkers.