Early Detection Of Smoking-Induced Pulmonary Alterations Using Hyperpolarized ^{3}He MRI Derived Alveolar Partial Pressure of Oxygen

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INTRODUCTION: Hyperpolarized gas MRI was introduced over a decade ago to estimate the alveolar partial pressure of oxygen (p_AO_2). However, it has never been systematically investigated for its value as either a diagnostic tool or as a tool for monitoring disease progression and response to new therapies. In this work, the imaged p_AO_2 is compared with the pulmonary function test (PFT), Six Minute Walk Test (6MWT) and St. George Respiratory Questionnaire (SGRQ) results and a logistic regression model is developed to predict the *asymptomatic smokers*.

METHODS: 43 human subjects, separated in three groups (10 Healthy Nonsmokers; 16 Asymptomatic Smokers and 17 COPD), underwent p_AO_2 imaging followed by a PFT and 6MWT.They were also asked to fill out a SGRQ. A multi-slice, four time-point scheme presented in [1] was performed across twelve 13-mm coronal slices after a single breath of HP gas. This method used an interleaved acquisition scheme with a gradient echo imaging pulse sequence at a spatial resolution of 8.3×8.3 mm^2 (T_R/T_E = 6.7/3.2 ms, FOV = 30×40 cm^2, flip-angle = ~5°, Slice-Gap = 20%). A normoxic mixture of ^{3}He:N_2:O_2 (3:1:1) based on subjects' total lung capacity was administered with images acquired during a 12-sec end-inspiratory breath-hold. The whole-lung p_AO_2 averages and standard deviations (Mp_AO_2±Dp_AO_2) were computed. Univariate *Pearson* correlations were used to analyze the relationship between MRI measures of respiratory function and non-imaging measurements. A stepwise multivariate logistic regression was performed for the prediction of "*asymptomatic smoker*" status. A p_R=0.25 was considered for a predictor to retain in the multivariate regressions. A Leave-one-out method was used for cross-validation. An alpha level of 0.05 was considered significant in all analyses.

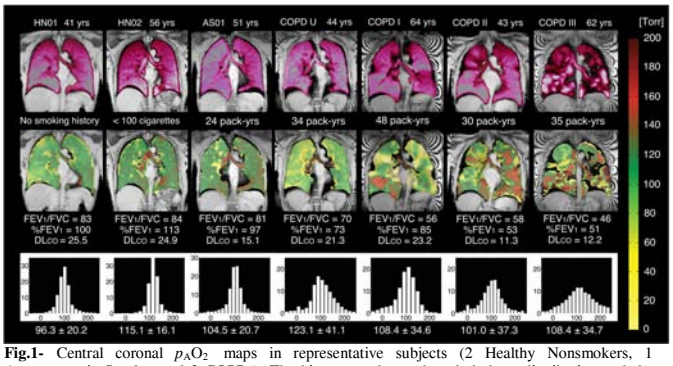

Fig.1- Central coronal p_AO_2 maps in representative subjects (2 Healthy Nonsmokers, 1 Asymptomatic Smoker and 3 COPDs). The histogram shows the whole-lung distribution and the mean and standard deviation was extracted from a Gaussian fit to the histograms. The PFT metrics, age and smoking history is listed for comparison.

RESULTS & DISCUSSION: The three cohorts were not significantly different with respect to age and BMI. Figure 1 shows the central coronal ^{3}He MRI static ventilation maps for representative subjects and the corresponding oxygen-weighted maps and histograms. Figure 2 illustrates the correlation between imaging and non-imaging markers. The AS subjects had significantly higher p_AO_2 heterogeneity compared to the HNs (p<0.001) and had significantly lower Dp_AO_2 when compared to the COPD subjects (p<0.001). There were no differences in the global oxygen tension averages (Mp_AO_2) between the healthy subjects and smokers (p=0.251). The COPD subjects had elevated Mp_AO_2 compared to smokers (p=0.016). A strong negative correlation was observed with FEV_1/FVC and FEV_1 % predicted. A moderate negative correlation was observed with DL_{CO}, which is a measure of gas exchange quality in the lungs. The SGRQ scores significantly associated with the Dp_AO_2. Subjects' 6MWT distance moderately correlated with Dp_AO_2. The pack-years smoking directly and strongly related to the oxygen-tension heterogeneity. A stepwise multivariable logistic regression analysis was performed to predict the "*asymptomatic smoker*" status. The standard PFT parameters of the GOLD criteria (FEV_1/FVC, %FEV_1) as a measure of obstruction, DL_{CO} as an indication of emphysema, the distance travelled in 6MWT, and the SGRQ overall score, along with imaging markers, were selected to enter the univariate logistic regressions between. Smokers can be distinguished from the healthy nonsmokers by their significantly increased p_AO_2 heterogeneity and slightly lowered FEV_1/FVC (p=0.029), which both retained in the final model. Mp_AO_2, 6MWTD, and SGRQ score also passed the test to enter the multivariable analysis (p_E<0.25) but were not retained in the final model. DL_{CO} entered the model as a confounding variable (p= 0.092) and significantly improved the model (p=0.035). After scaling of each variable, the odds ratios were calculated. The final estimates and odds for the "*asymptomatic smoker*" status, together with the statistical results of the logistic regression are presented in Table 1. Figure 3 shows the two-dimensional scatter plots and the 95% confidence ellipses of each cohort/variable pair combination. It is evident that the Dp_AO_2 has an effective role in classification, since the overlaps are minimized in the rows containing Dp_AO_2. The area under the receiver operating characteristic curve (AUC) for the logistic regression model was 0.902.

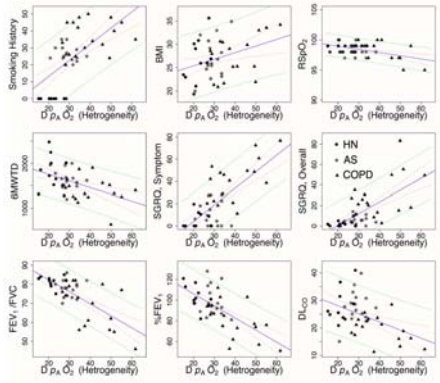

Fig.2- The p_AO_2 maps for the representative COPD subject **(a)** for the conventional single-breath regime and **(b)** for the presented multi-breath protocol.

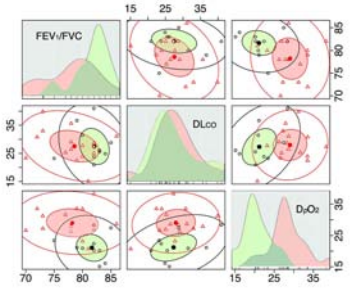

Fig. 3- Scatter plots and 2D distribution ellipses of HN and AS subjects for pair variables retained in the logistic regression model (FEV1/FVC, DLCO and DpAO2). The outer ellipses show the 95% confidence intervals. (Green: HN and Red: AS subjects).

Table 1- Multivariate Regression (prediction of *Assymptomatic Smokers*)

Variable	*Coeff.*	SE	OR*	95% CI*	z	P > |z|
DpO_2	0.818	0.387	1.15	(1.047 , 1.359)	2.12	**0.034**
FEV_1/FVC	-0.240	0.208	0.92	(0.776 , 1.043)	-1.16	**0.247**
DL_{co}	-0.288	0.171	0.87	(0.697 , 0.997)	-1.68	**0.092**

Abbreviations: *Coeff.* (Coefficient), SE (standard error), OR (odds ratio), CI (confidene - interval), G-statistic (likelihood ratio test), z-statistic (Wald test).
* The odds ratios for the final model is based on the scaled varaibles; DpO_2 per 6 Torr, FEV_1/FVC per 3%, DL_{CO} per 2 ml/min/mmHg and 6MWTD per 100 ft.

CONCLUSION: This study set out to develop a more precise means of detecting, staging, and evaluating early respiratory symptoms of COPD using a functional HP-MRI technique. It is anticipated that using this technology to measure alveolar oxygen tension would help to detect the small, difficult-to-assess functional alterations characteristic of smoking-induced COPD with greater sensitivity than traditional techniques.

REFERENCES: [1] Hamedani H. et al. Magn. Reson. Med. 2012; 67:1332–1345.