Repeatability Study of Regional Measurements of Alveolar Oxygen Tension in Humans by Hyperpolarized ^{3}He MRI

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INTRODUCTION: Reliable imaging of regional alveolar oxygen tension (p_AO_2) in human lungs is a useful probe for investigating a variety of pulmonary diseases and is also beneficial for monitoring efficacy of emerging respiratory therapeutics. p_AO_2 as a physiological measure of ventilation/perfusion and gas exchange is a fluctuating functional metric and function of physiological conditions under which the measurements are performed. This renders the reproducibility of p_AO_2 measurements a crucial step towards establishing it as biomarker. The goal of this study was to develop an intraclass measure of test-retest reliability/repeatability for imaging p_AO_2 in human lungs using hyperpolarized (HP) ^{3}He oxygen-weighted MRI during a two-week time period.

METHODS: Four healthy non-smokers (3 F, 56±2 yrs, BMI=26.3±3.1) and four asymptomatic smokers (3 M, 52±8 yrs, BMI=26.5±4.6) participated in repeated p_AO_2 imaging three times over in a two-week period. Before each MRI session, pulmonary function testing (PFT) was performed on subjects. p_AO_2 imaging was performed over twelve 13-mm coronal slices with 20% interslice gap, using an interleaved acquisition scheme [Hamedani *et al.* MRM 2011] with a gradient echo imaging pulse sequence (spatial resolution 8.3×8.3×15.3mm^3, TR/TE=6.7/3.2ms, FOV=30×40cm^2, α=5˚). 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. At the end, exhaled gas was collected for measuring the end-tidal oxygen and carbon dioxide concentrations (ETO_2 and $ETCO_2$). For validation of imaged p_AO_2, the whole-lung p_AO_2 mean (μ_{pAO2}) were regressed on expected p_AO_2 for each measurement using the Alveolar Gas Equation and based on measured ETO_2 and $ETCO_2$, Respiratory Quotient=0.8 and Bohr equation with a weight-based estimation for dead-space. The repeatability of imaged whole-lung μ_{pAO2} and dispersion (σ_{pAO2}) in three different days were compared for each subject. To formally test the empirical regional repeatability, isotropic bins of p_AO_2 maps (3×3×3 cm^3) for each lung over three days were fitted using a mixed-effects linear model regressed on fixed effects including a subject group factor, a gradient term by slice, weight, sex, and BMI. All insignificant covariates were excluded after regression. It can be assumed that p_AO_2 will be more correlated within subjects than between subjects and will be more correlated within slices that between slices, also that voxels within a slice will be more correlated than those between slices. So, the subject, slice, voxel, days and residual errors were used to estimate the conditional intra-class correlation coefficients.

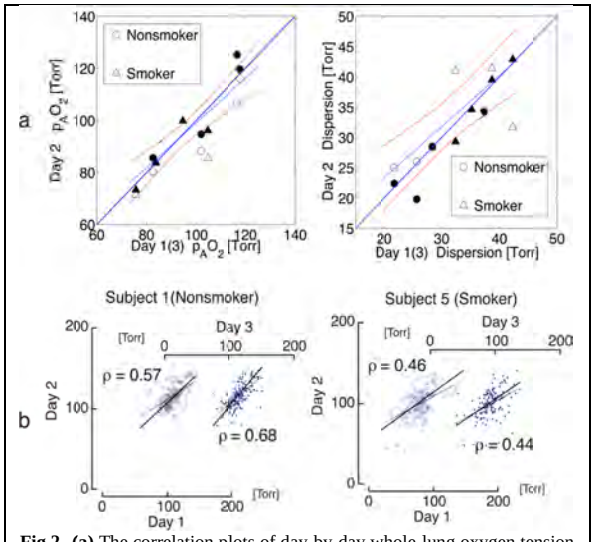

Fig.2- (a) The correlation plots of day-by-day whole-lung oxygen tension mean and dispersion for all subjects. The vertical axis shows day2 and horizontal one has both day1 and day3. The hollow markers are day1-day2 and the rigid ones are day2-day3. **(b)** The ROI-based correlation plots for representative subjects. Day-by-day correlation plots of day1-day2 and day1-day3 in one plot.

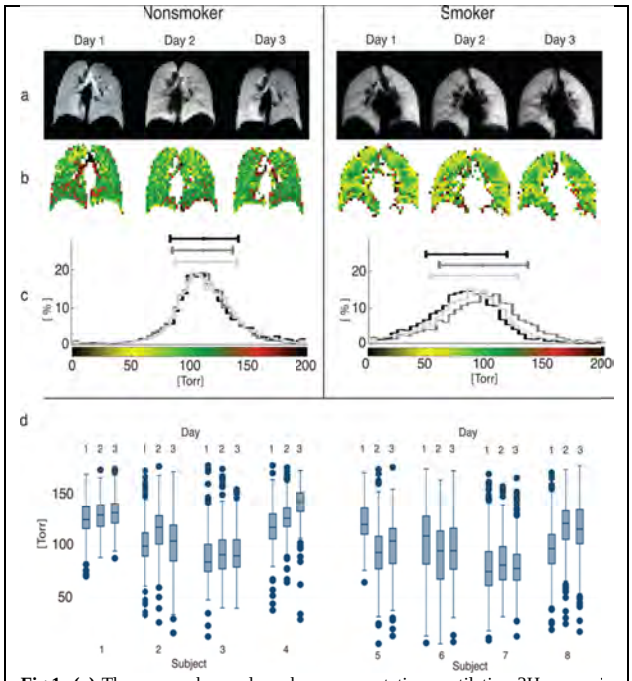

Fig.1- (a) The nonsmoker and smoker representative ventilation 3He maps in three different days in a middle slice. **(b)** The oxygen tension maps for the same ventilation maps. **(c)** The superimposed whole-lung histograms of the representative subjects in three days. The lines above the histograms show the mean and standard deviation. **(d)** The summary of all the measurements in all subjects as box plots.

RESULTS:

Fig.1(a,b) shows three repetitions of ventilation and p_AO_2 maps for a representative slice in a healthy nonsmoker and an asymptomatic smoker subject. **Fig.1(c)** shows the corresponding whole-lung p_AO_2 histograms (all the three days superimposed). **Fig.1(d)** summarizes all subjects' p_AO_2 distributions as boxplots.

Regressing the expected p_AO_2 on μ_{pAO2} gives a slope of 0.95 (95% CI: 0.91, 1.00; P < 0.001). The dispersion (σ_{pAO2}) in nonsmokers is significantly less than smokers (r = 0.58; 95% CI: −0.04, 0.87; P < 0.001) and correlates well with Forced Expiratory Flow (r = −0.64; 95% CI: −0.93, 0.12; P = 0.043). **Fig.2(a)** shows the day by day whole lung μ_{pAO2} and σ_{pAO2} correlation plots, and **Fig.2(b)** illustrates the regional day-by-day correlations for the isotropic bins for two representative subjects. The average slope of these ROI-based day-by-day regressions is 0.68±0.15 for all subjects (nonsmokers: 0.78±0.14, smokers 0.59±0.12). **Table 1** summarizes the results of mixed-effect model. The constant fixed effect coefficient is the average p_AO_2 among all the subjects in the binned data. There is a position-dependent gradient with oxygen levels falling by 1.3 Torr for each binned slice. The model also proves that smokers had significantly lower pulmonary oxygen levels than nonsmokers. Subject variability was small at 11.03 Torr and of interest was the observation that the variation between slices was much smaller than the variation between voxels within a slice. The random effects indicate that the nonsmoker and smoker residuals are 15.27 and 19.28, suggesting the scatter increases with smoking. Finally, the intraclass correlation for nonsmokers and smokers was 0.71 and 0.59, respectively.

		Coefficient [Torr]	Standard Error [Torr]	P-value	95% CI [Torr]
Fixed Effects	Constant	109.16	5.97	< 0.01	(97.46, 120.85)
	Slice	-1.31	0.62	0.03	(-2.51, -0.10)
	Smokers	-18.05	7.6	0.02	(-32.95, -3.15)
		Est. SD			
Residuals	Subject	11.3	2.75		(6.77, 17.97)
	Slice	5.25	0.76		(3.95, 6.98)
	Voxel	12.35	0.35		(11.69, 13.05)
	Normal	15.27	0.98		(14.88, 15.67)
	Smoker	19.28	0.27		(18.76, 19.82)

Table 1. The mixed effect model results.

CONCLUSION: The proposed imaging method provides a p_AO_2 map of the entire lung at sub-centimeter spatial resolution in a single breath-hold of a normoxic mixture of HP ^{3}He. The observed variability of p_AO_2 is partly related to physiology differences between subjects, days and different slices but experimental errors should also be mentioned. Challenges of gas administration, subject's movements, and early gas flow and diffusion between slices as well as the high sensitivity of p_AO_2 measurement to signal to noise should be counted as other sources of uncertainty. Results show that this HP gas MRI technique provides a very promising global repeatability and reasonable reproducibility in regional estimate of alveolar oxygen tension in both groups. The dispersion in oxygen distribution could also be mentioned as a marker for distinguishing the smokers.