A Large-scale Regional Reproducibility Study of Hyperpolarized ^{3}He Alveolar Oxygen Tension in Human Subjects

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Introduction: Pulmonary gas exchange is the most crucial function of lungs and yet is most altered in nearly all respiratory diseases. Measurement of gas exchange, especially on a localized basis, is therefore of great interest to the medical community for monitoring patient condition as well as assessing the therapeutic outcome. Hyperpolarized (HP) noble gas MRI represents one of the few noninvasive methods capable of measuring regional pulmonary gas exchange. In this work we present the first large-scale short-term human gas exchange imaging reproducibility study using this technology. We used HP ^{3}He derived regional alveolar oxygen tension (P_AO_2) as a measure of gas exchange and studied its regional variability and reproducibility in two groups: asymptomatic smokers (AS) and healthy non-smokers (HNS). We also discuss the effects of SNR and physiologic variability on the reproducibility parameters of interest.

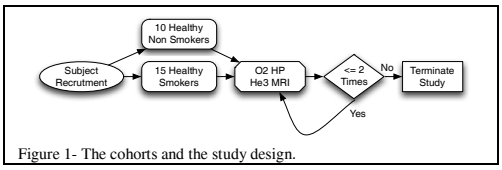

Figure 1- The cohorts and the study design.

Methods: The study design is illustrated in Fig. 1 and the data processing plan is shown in Fig. 2. 10 HNS and 15 AS (>20 pack year, normal PFT, no other health conditions) were recruited for this study. Each subject was physically examined, received pulmonary function testing, and underwent HP ^{3}He MRI protocol as described in Hamedani *et al.* [1] twice in the same imaging session. Four consecutive series of 12 coronal slices were acquired per measurement using a gradient echo pulse sequence during a 15-s breath hold with FOV = 40×30 cm^2; ST = 13 mm; interslice gap = 20% of ST; $\alpha_{nominal} = 5°$; MS = 48×36; T_R/T_E = 6.69/3.1 ms. Subjects inhaled a HP ^{3}He/N_2/O_2 mixture (F_iO_2~21%). The inhaled volume was controlled at 12% of the subject's TLC using a custom-made gas delivery device. Subjects were monitored to ensure physiologic stability during the study. A commercial polarizer (GE Healthcare) was used to generate the HP ^{3}He gas at 20–30% polarization. Oxygen values were reconstructed as described in [1]. An affine-based algorithm was used to coregister each subject's P_AO_2 maps. The imaging voxels were then binned into isotropic 3.3×3.3×3.1 cm^3 regions of interest (ROI). The most anterior and posterior images were excluded from the analysis due to SNR and partial volume effects. We accounted for the subjects, slices, and ROI variability as the random-effects for both AS and HNS cohorts using a mixed linear model. Two models were constructed, one for each cohort, using a bottom up approach and log likelihood ratio tests. Only significant covariates were considered. Results were used to derive an intra-class correlation coefficient that serves as our measure of reproducibility. Due to the effect of SNR on measurement uncertainty, subjects used in the analysis were matched based on their average SNR in a case controlled fashion with 10 subjects from each group. The remaining five AS subjects not included in the comparison analysis were separately analyzed to contrast the effect that changes in average SNR has on measurement variability. The bootstrap sampling method was used to compare study groups.

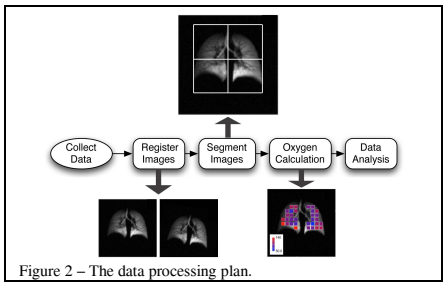

Figure 2 – The data processing plan.

Table 1. Fixed Effect

Asymptomatic Smokers				
Coefficient	Estimate (Torr)	SE (Torr)	*P* value	95% CI (Torr)
Constant	101.16	4.08	<0.001	(93.15,109.16)
Healthy Non-smokers				
Constant	102.28	4.63	<0.001	(93.20,111.37)
Slice	−14.67	3.95	<0.001	−(22.41,6.93)
Slice^2	2.19	0.64	0.001	(0.93,3.45)
SE: standard error; CI: confidence intervals.				

Results and Discussion: The regression results are presented in Tables 1 and 2. From the fixed components we note that the average (i.e., constant) term agrees with the average values predicted by the alveolar gas equation and that AS and HNS values are statistically equivalent. We also see that the HNS subjects demonstrate the expected gravity-dependent oxygen gradient, while the smokers do not, suggesting that while the HNS appear healthy there are *measureable* physiologic changes brought about by the chronic smoking process. The random effects show that there is similar variability between the AS and HNS subjects implying excellent case control matching. The intra-slice variability is similar; in addition, AS have greater intra-pixel variability, confirming the supposition that the distribution of gas exchange in AS lungs is more heterogeneous than that of HNS lungs. The AS residual term is higher than that of HNS demonstrating a greater intra-measurement scatter in smoking lungs, i.e. AS physiologically have greater temporal variation in regional gas exchange than HNS. This observation is formalized by the intra-class correlation coefficient for AS and HNS, which we found to be 0.65 and 0.67, respectively. This represents our measure of repeatability and is the central finding of this work. The correlation coefficient between the AS and HNS average SNR ratio was 0.97, suggesting excellent case-controlled matching and that the changes seen between cohorts is not due to SNR differences. The binned average SNR for AS and HNS groups were 704 and 736, respectively (t-test comparison of SNR $t(9) = -0.63$; $P = 0.55$). The binned average SNR for the remaining five AS subjects was 987 (34% larger). Reanalyzing this cohort of patients shows that the residual variance falls to 10.95, and that the intra-class correlation coefficient increases to 0.82. Our results indicate that temporal variability is dominated by physiologic variation and measurement noise, and that repeatability can be improved substantially by increasing imaging SNR. It is also evident that P_AO_2 measurements would benefit greatly from increased polarization levels.

Table 2. Random Effects

Asymptomatic Smokers			
Parameters (SD)	Estimate (Torr)	SE (Torr)	95% CI (Torr)
Subject	12.50	3.16	(7.62,20.51)
Slice	6.37	0.91	(4.82,8.43)
Pixel	11.85	0.46	(10.98,12.78)
Residual	13.38	0.29	(12,82,13.95)
Healthy Non-smokers			
Parameters (SD)	Estimate (Torr)	SE (Torr)	95% CI (Torr)
Subject	11.49	3.03	(6.86,19.26)
Slice	8.43	1.03	(6.64,10.71)
Pixel	7.93	0.39	(7.19,8.73)
Residual	11.44	0.24	(10.98,11.93)

Conclusion: We estimated the short-time reproducibility of regional P_AO_2 measurements by HP ^{3}He MRI in asymptomatic smokers and non-smokers. We found that the repeatability is similar in AS and HNS and a strong function of measurement noise. We also showed that asymptomatic smokers, while appearing normal from the physical exam and PFT standpoint, show demonstrable difference in temporal and spatial imaging characteristics.

REFERENCES: [1] Hamedani *et al.*, MRM 2011: doi:10.1002/mrm.23125