INTRODUCTION: Reliable imaging of regional alveolar oxygen tension (pO2) 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. pO2 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 pO2 measurements a crucial step towards establishing it as a biomarker. The goal of this study was to develop an intra-class measure of test-retest reliability/reproducibility for imaging pO2 in human lungs using hyperpolarized (HP) 3He 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 pO2 imaging three times over a two-week period. Before each MRI session, pulmonary function testing (PFT) was performed on subjects. pO2 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 8.38x3.915.3mm, TR/TE=6.7/3.2ms, FOV=30x30x30cm, n=5). A normoxic mixture of 98.99.9% N2O, 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 (ETO2 and ETCO2). For validation of imaged pO2, the whole-lung pO2 mean (μpO2) were regressed on expected pO2 for each measurement using the Alveolar Gas Equation and based on measured ETO2 and ETCO2. Respiratory Quotient=0.8 and Bohr equation with a weight-based estimation for dead-space. The repeatability of imaged whole-lung μpO2 and dispersion (σpO2) in three different days were compared for each subject. To formally test the empirical regional repeatability, isotropic bins of pO2 maps (3x3x3 cm3) 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 pO2 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.

RESULTS: Fig.1(a,b) shows three repetitions of ventilation and pO2 maps for a representative slice in a healthy nonsmoker and an asymptomatic smoker subject. Fig.1(c) shows the corresponding whole-lung pO2 histograms (all the three days superimposed). Fig.1(d) summarizes all subjects’ pO2 distributions as boxplots. Regressing the expected pO2 on μpO2 gives a slope of 0.95 (95% CI: 0.91, 1.00; P<0.001). The dispersion (σpO2) 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 μpO2 and σpO2 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 pO2 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.

CONCLUSION: The proposed imaging method provides a pO2 map of the entire lung at sub-centimeter spatial resolution in a single breath-hold of a normoxic mixture of HP 3He. The observed variability of pO2 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 pO2 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.