Gas Uptake Measures on Hyperpolarized Xenon-129 MRI are Inversely Proportional to Lung Inflation Level

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Target audience: Physicians and scientists interested in functional lung imaging or lung diseases.

Introduction: Gas uptake measures from hyperpolarized xenon-129 (Xe129) MRI show high sensitivity to alterations of lung function in subjects with lung diseases such as COPD, asthma[1,2], or idiopathic pulmonary fibrosis[3]. Previous studies have shown a strong dependence of these measures on lung inflation[2,3]. The purpose of this study was to investigate the quantitative relationship between gas uptake measures and lung inflation level.

Methods: The study group included 12 healthy subjects, separated into a younger group (N=5, age 20-27, FEV_1 %pred 97%±6%, FEV_1/FVC 0.85±0.05) and an older group age-matched to COPD subjects (N=7, age 44-70, FEV_1 %pred 94%±6%, FEV_1/FVC 0.78±0.05), and 5 subjects with COPD (C1-C5, age 56-74, FEV_1 %pred 67%±21%, FEV_1/FVC 0.54±0.17). To quantitatively measure the lung inflation level during gas uptake imaging, subjects underwent a combined Xe129 dissolved-phase[1] and proton acquisition in a single breath hold. Each subject was imaged at three lung inflation levels: 1.) total lung capacity (TLC); 2.) one-third of forced vital capacity (1/3 FVC, based on spirometry) from maximal exhalation; and 3.) smallest lung-volume reachable by the subject (RV for healthy subjects, somewhat larger than RV for most COPD subjects). Sequence parameters for the Xe129 acquisition were the same as previously described[1] (acquisition time 11 s), except for a lower spatial resolution (15.2x15.2x17.6 mm^3) to ensure sufficient signal-to-noise ratio. Four gas uptake measures were calculated: total dissolved-phase-to-gas (DP-to-gas), tissue-to-gas, red-blood-cell (RBC) to gas and RBC-to-tissue. A 3D proton gradient-echo sequence was used to measure the lung volume following the dissolved-phase acquisition in the same breath hold (Fig. 1). Two additional proton image sets were acquired independently to measure TLC and RV. Proton image resolution was 5.2x3.9x6.0 mm^3, interpolated to 3.9x3.9x3.9 mm^3, and the acquisition time was 4 s. The lung region was first segmented using a multi-atlas label fusion approach[5] and then manually refined, if needed, for an accurate quantification of the lung volume (Fig. 1). Linear regression was used to investigate the relationship between lung inflation level and the gas uptake measures. Healthy subjects were analyzed as two groups (younger and older), while the COPD subjects were analyzed individually. MR studies were performed at 1.5T (Avanto; Siemens) using a flexible Xe129 chest RF coil (Clinical MR Solutions). Enriched xenon gas (87% Xe129) was polarized using a prototype commercial system (XeBox-E10, Xemed).

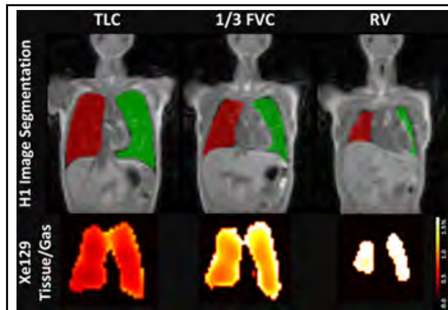
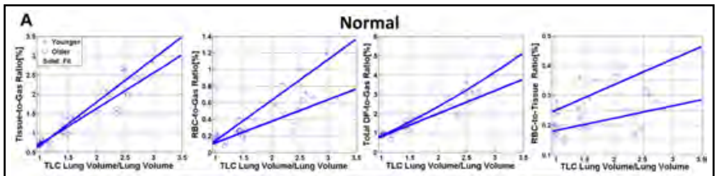


Figure 1. Results from the combined Xe129 dissolved-phase and proton acquisition in a healthy subject. The upper row shows coronal proton images acquired at three inflation levels and the associated segmented lung regions (red: right lung, green: left lung). The lower row depicts the corresponding measured tissue-to-gas ratio maps. Higher tissue-to-gas ratios were measured at lower lung inflation levels, as expected.



Normal		Tissue/Gas	RBC/Gas	Total DP/Gas	RBC/Tissue
Younger	r	0.99	0.97	0.98	0.81
	p	<0.001	<0.001	<0.001	0.003
	k	1.13	0.49	1.62	0.087
Older	r	0.92	0.90	0.93	0.58
	p	<0.001	<0.001	<0.001	0.012
	k	0.93	0.26	1.19	0.042

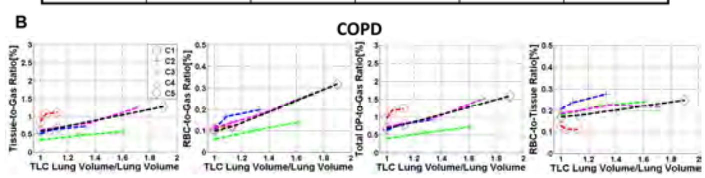


Figure 2. Lung inflation level (ratio of TLC lung volume over lung volume at which Xe129 images were acquired) versus measured whole-lung tissue-to-gas, RBC-to-gas, total DP-to-gas, and RBC-to-tissue ratios for healthy subjects (A) and subjects with COPD (B). Healthy subjects were divided into two groups (younger and older) and investigated using linear regression. The regression fits are solid blue lines in the figures. The correlation coefficient *r*, significance *p* and slope *k* of the regression line are shown in the table for each group. Dashed lines in B connect the individual data points for the COPD subjects.

Results & Discussion: In healthy subjects, we found strong inverse relationships between lung inflation level and the measured tissue-to-gas, RBC-to-gas and total DP-to-gas ratios for both the younger and older groups ($r \geq 0.9$, $p < 0.001$, Fig 2). This is reasonable because all of these dissolved-phase-to-gas ratios are positively correlated with the alveolar surface-to-volume ratio, which decreases when lung inflation level increases. The inverse relationship found between lung inflation level and the RBC-to-tissue ratio (Fig. 2), although not as strong as those for the other three ratios, could be caused by changes in lung blood volume and/or pulmonary venous flow due to changes of the transpulmonary pressure, consistent with the literature[6]. The slopes of the regression lines for the younger group were all higher than those for the older group, which means the younger subjects had higher tissue-to-gas and RBC-to-tissue ratios than the older subjects at the same lung inflation level. Previously, hyperpolarized helium-3 diffusion MRI studies have shown that the helium-3 ADC values increases with increasing subject age[7], which could explain the lower tissue-to-gas ratios observed in older subjects because of decreased tissue density or surface-to-volume ratios. The decrease of the RBC-to-tissue ratios with age could be caused by a decreased cardiac output[8].

Based on the findings in healthy subjects, we assumed that the gas uptake measures for COPD subjects would also be inversely proportional to their lung inflation levels. As seen in Fig. 2B, this was in general the case, although there were greater differences among subjects compared to healthy groups, as might be expected given the variation of disease among subjects (GOLD stage 1 to 3). Therefore regression analysis was not performed for the COPD group, and instead the linearity for individual COPD subjects was evaluated by using the gas uptake measures at the highest (TLC) and lowest lung inflation levels to predict the gas uptake values measured at intermediate inflation level. The relative errors of the predicted values were calculated by comparison with the actually acquired gas uptake measures. The mean and standard deviation of the absolute values of relative errors for the predicted tissue-to-gas, RBC-to-gas, total dissolved-phase-to-gas and RBC-to-tissue ratios were 7.7% ± 6.5%, 9.2% ± 6.9%, 8.1% ± 5.6%, and 6.6 ± 3.1%, respectively.

Conclusion: Strong inverse relationships were found between gas uptake measured by Xe129 MRI and lung inflation levels. These findings could be used to obtain normalized lung function parameters that are independent of the lung inflation level at which they were measured.

References: [1] Qing K, et al. J. Magn. Reson. Imaging, 2014. [2] Qing K, et al. NMR Biomedicine, 2014. [3] Kaushik SS, et al. J. Appl Physiol, 2014. [4] Tsao J, et al. Magn.Reson. Med, 2013. [5] Wang H, et al. IEEE Trans Pattern Anal Mach Intell, 2013. [6] Brower R. et al. J. Appl Physiol, 1985. [7] Altes, TA, et. al. J. Magn. Reson. Imaging, 2006. [8] Brandfonbrener M, et al. Circulation, 1955. **Acknowledgement:** Supported by NIH grant RO1 HL109618 and Siemens Medical Solutions.