

Establishing Biomarkers of Gas-Transfer Using Hyperpolarized ^{129}Xe Dissolved-Phase Spectroscopy in Healthy Volunteers and Subjects with Pulmonary Fibrosis

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Target Audience: Hyperpolarized ^{129}Xe MRI, Clinical Functional Lung Imaging

Purpose: Inhaled hyperpolarized (HP) ^{129}Xe readily dissolves in pulmonary blood and tissues where it exhibits two distinct resonances in the barrier tissues and plasma (197 ppm) and in the RBCs (217 ppm). These resonances have emerged as a promising surrogate to measure pulmonary gas-transfer across the blood-gas barrier¹⁻³. In standard clinical practice, such measurements are made using the dilution of carbon monoxide (DL_{CO}), but this metric is sensitive to subject compliance and is plagued by variability across institutions. Here we propose a biomarker of gas-transfer, based on global HP ^{129}Xe spectroscopy. We establish baseline values in healthy normal volunteers and show that it is dramatically reduced ^{129}Xe gas transfer in subjects with pulmonary fibrosis (PF).

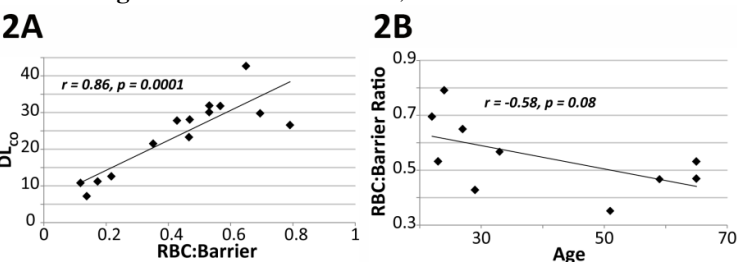
Methods: ^{129}Xe gas transfer spectra were acquired in 10 healthy volunteers and 5 subjects with pulmonary fibrosis (PF). Each subject received 200-ml of enriched ^{129}Xe , polarized to 9-12% and diluted with 800-ml of N_2 . The single-breath acquisition began with 200 spectra acquired on the dissolved-phase resonances at +3832 Hz above the gas-phase resonance, followed by one dedicated gas-phase reference spectrum. Spectra were taken with 512 points, bandwidth = 8/15.63 kHz, sinc pulse length = 1200 μs , flip-angle of $\sim 15^\circ$. The first 100 dissolved-phase spectra contain signal from ^{129}Xe in the larger vasculature, and were hence discarded. The last 100 dissolved-phase spectra were averaged together, and along with the single gas-phase spectrum were fit to Lorentzian functions to extract the area under the curve (AUC) for each resonance. These AUCs were used to calculate the ratios of RBC-Barrier, Barrier-Gas, and RBC-Gas, which were then correlated with DL_{CO} and subject age. The ratios were tested for significance using the Wilcoxon Rank-sum test and the correlations, were evaluated using the Student's T-test.

Results and Discussion: Figure 1A shows a dissolved-phase spectrum from a healthy volunteer and a subject with PF, showing greatly diminished RBC uptake. As shown in Figure 1B, for healthy volunteers, the mean RBC-Barrier ratio was 0.55 ± 0.13 , whereas for PF subjects this was reduced more than 3-fold to 0.15 ± 0.04 ($p=0.0007$). Using the gas-phase reference spectra, we determined that the reduced RBC-Barrier ratio in PF subjects was attributable partially to a 2.3-fold lower RBC signal ($p=0.008$), and partially to a 1.4-fold increase in Barrier signal ($p=0.075$). As shown in figure 2A, the RBC-Barrier ratio correlated significantly with DL_{CO} ($r=0.86$, $p=0.001$) and also exhibited a modest correlation with subject age. That is, RBC:Barrier ratio diminished in older subjects ($r=-0.58$, $p=0.075$).

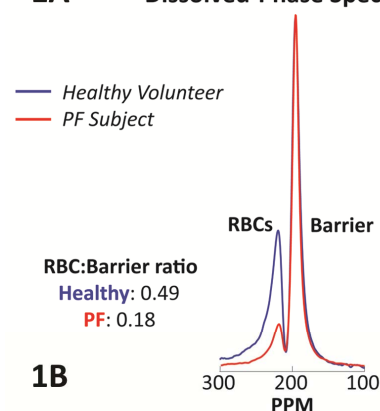
Conclusions: The RBC:Barrier ratio obtained through ^{129}Xe spectroscopy shows a consistent and reproducible⁴ reduction in subjects with pulmonary fibrosis relative to healthy controls. Despite operating on completely different physical principles, ^{129}Xe spectroscopy correlates well with conventional DL_{CO} . However, because ^{129}Xe spectroscopy does not rely on the physical consumption of gases, and is inherently “self-calibrating” by virtue of its 3 distinct resonances, the technique is likely to be less dependent on subject cooperation, and may be more reproducible across clinical sites. Most importantly, this global indicator of alveolar diffusion limitation is now being extended to an imaging metric so that gas-transfer impairment can be visualized regionally.

References: 1. Cleveland *et al.*, PloS ONE 2010. 2. Mugler *et al.*, PNAS 2010. 3. Kaushik *et al.*, JAP 2013. 4. Kaushik *et al.*, Am J Respir Crit Care Med, 2013

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1A Dissolved-Phase Spectrum



1B

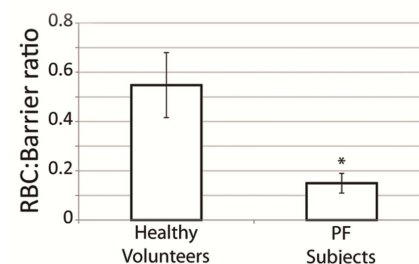


Figure: (1A) The dissolved-phase spectrum in a healthy volunteer and a subject with pulmonary fibrosis showing a ~3-fold reduction in the RBC peak. The mean RBC:Barrier ratio is shown in figure 1B. (2A) RBC:Barrier ratio correlated significantly with subject DL_{CO} ($r=0.86$) and moderately with subject age.