Regional Mapping of Gas Uptake by Lung Tissue and Blood in Subjects with COPD using Hyperpolarized Xenon-129 MRI

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Target audience: Physicians and scientists interested in functional lung imaging or chronic obstructive pulmonary disease (COPD).

Introduction: COPD is a complex disease with several disease processes progressing together or independently, such as airway obstruction, tissue destruction, loss of blood flow, inflammation and airway remodeling[1]. Hyperpolarized xenon-129 (Xe129) dissolved-phase imaging[2], which provides 3-dimensional mapping of both ventilation (airflow) and gas uptake by tissue and blood in the human lung, could be a useful tool to characterize lung function in COPD. The purpose of this study was to measure gas uptake of inhaled Xe129 in subjects with COPD and healthy controls, and to correlate the results with Xe129 ventilation imaging, diffusion-weighted imaging (DWI), pulmonary function tests including spirometry and diffusion capacity (DLCO), and exercise tolerance test (6 minute walk - 6MW).

Methods: Nineteen COPD subjects (age 51-83, FEV_1 %pred 64%±19%, FEV_1/FVC 0.59±0.15) and 21 healthy controls (age 22-56, FEV_1 %pred 77%±18%, FEV_1/FVC 0.65±0.10) underwent Xe129 dissolved-phase imaging using the protocol described in ref. 2. The Hierarchical IDEAL method[3] was used to separate the tissue and red-blood-cell (RBC) components from the multi-echo dissolved-phase images. For quantitative comparison among subjects, four ratios were generated as the gas uptake measures: total dissolved-phase-to-gas, tissue-to-gas, RBC-to-gas and RBC-to-tissue. Furthermore, all COPD subjects underwent combined Xe129 ventilation/H1 anatomical imaging, DWI, spirometry, DLCO, and 6MW tests. A co-registered 2D multi-slice spiral sequence (resolution: 3.9x3.9x15 mm^3) was used for the combined Xe129/H1 acquisitions (Xe129: TR/TE: 11.4/1.19 ms, acquisition time: 2.4 s; H1: TR/TE: 4.78/0.88 ms; acquisition time: 1.7 s). Lung regions were segmented based on relative ventilation using an automatic algorithm[4]. The percentage of poorly ventilated lung (V_{def} = volume of poorly ventilated lung / total lung volume) was produced for each subject. Acquisition parameters for DWI were TR/TE 13.8/9.4 ms, flip angle 8.5°, voxel volume 6x6x25 mm^3, *b* values 0 and 10 s/cm^2. For all Xe129 studies, subjects inhaled 1-L of xenon mixed with N_2 for a volume equaling 1/3 of their forced vital capacity based on spirometry. MR studies were performed at 1.5T (Avanto; Siemens) using a flexible Xe129 chest RF coil (Clinical MR Solutions), under a physician's IND for hyperpolarized Xe129 MRI. Enriched xenon gas (87% Xe129) was polarized using a prototype commercial system (XeBox-E10, Xemed). Pearson correlation was used to investigate the correlations among whole-lung measures generated from imaging acquisitions and clinical assessments.

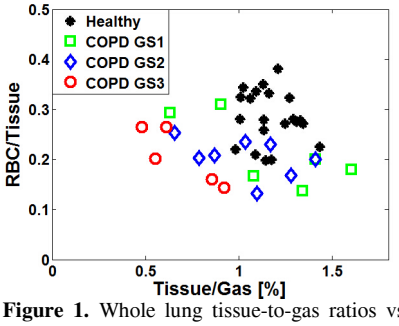

Figure 1. Whole lung tissue-to-gas ratios vs. RBC-to-tissue ratios acquired in 19 COPD and 21 healthy subjects. COPD subjects exhibited either decreased tissue-to-gas ratios or decreased RBC-to-tissue ratios, or both.

Results & Discussion: The total dissolved-phase-to-gas ratios (1.07%±0.33%), representing overall Xe129 gas uptake in the lung, and the RBC-to-gas ratios (0.20%±0.06%), representing the amount of Xe129 gas reaching the pulmonary circulation for COPD subjects, were both lower than those for the healthy group (1.35%±0.15%, 0.33%±0.07%; $p \leq 0.001$). COPD subjects as a group exhibited decreased RBC-to-tissue ratios (COPD: 0.21±0.05; healthy: 0.28±0.05, $p<0.001$), which could be secondary to vascular pruning (less pulmonary blood flow or volume) or thickening of alveolar walls (thicker gas-blood barrier), and had decreased tissue-to-gas ratios (COPD: 0.98%±0.33%; healthy: 0.17%±0.33%, $p=0.02$), which could be secondary to loss of tissue integrity in emphysema or lung hyperexpansion (decrease surface-to-volume ratio), but there was individual variation in the degree of abnormality in these two parameters (Fig. 1 and 2). Both parameters were low in all of the most severe COPD patients (GOLD Stage 3).

The 6MW test results (mean distance walked) only correlated moderately with the FEV_1 %pred (r=0.47, p=0.04), and did not correlate with any other function test or Xe129 imaging result. The V_{def} values correlated more with FEV_1 %pred (r=-0.73, p<0.001) and FEV_1/FVC (r=-0.58, p=0.009) than with the FEV_{25-75} %pred (r=-0.49, p=0.03). As expected, the measured RBC-to-gas ratios were highly correlated with the DLCO over alveolar size (Va) ratios (DLCO/Va, r=0.71, p<0.001), since both measure the overall gas exchange efficiency from alveolar airspaces to the pulmonary blood. All whole-lung dissolved-phase-to-gas ratios including the tissue-to-gas, RBC-to-gas and total dissolved-phase-to-gas ratios were inversely correlated with the Xe129 apparent diffusion coefficient (ADC) (r=-0.79, p<0.001; r=-0.66, p=0.002; r=-0.80, p<0.001) in COPD subjects, which suggests the decrease of gas uptake in COPD is mainly due to enlargement of distal airways, emphysematous tissue destruction, and concurrent vascular pruning. Interestingly, we found that all three dissolved-phase-to-gas ratios and DLCO (measures of gas exchange) correlated with FEV_1/FVC (a measure of airflow obstruction) in these COPD subjects (tissue-to-gas: r=0.76, p<0.001; RBC-to-gas: r=0.67, p=0.002; total dissolved-phase-to-gas: r=0.77, p<0.001; DLCO/Va: r=0.64, p=0.003). Another interesting finding was that the measured RBC-to-tissue ratios in COPD did not correlate with any of the function tests or other Xe129 imaging results, suggesting that the RBC-to-tissue ratio could be an independent indicator of physiological factors, such as pulmonary perfusion or alveolar septal wall thickness, providing information unobtainable by the other measurements used in this study.

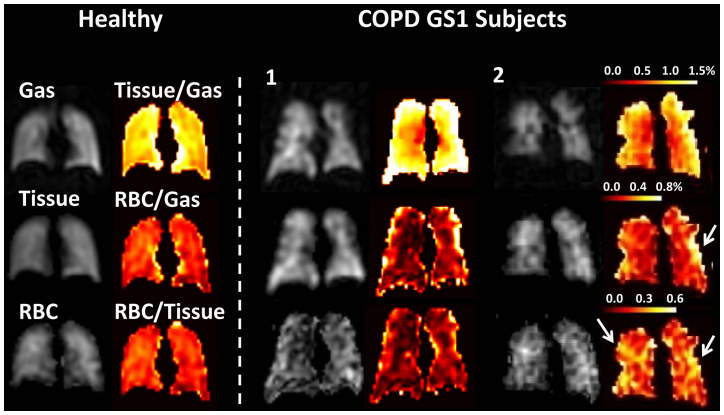

Figure 2. Representative Xe129 dissolved-phase MR images and ratio maps from one healthy subject and two COPD GOLD stage (GS) 1 subjects. As compared with the healthy subject (whole-lung mean tissue-to-gas ratio: 1.29%, RBC-to-gas ratio: 0.36%, RBC-to-tissue ratio: 0.28), COPD subject 1 had normal to slightly elevated tissue-to-gas ratios (mean 1.33%), and lower RBC-to-tissue and RBC-to-gas ratios (mean 0.14 and 0.18%), while COPD subject 2 had lower tissue-to-gas ratios (mean 0.90%), but regionally elevated RBC-to-gas and RBC-to-tissue ratios (arrows, whole-lung mean 0.28% and 0.31, in the normal range).

Conclusion: We found significant decrease of gas uptake in COPD subjects as compared to healthy controls. Although different patterns of functional alternations existed in COPD (decreased tissue-to-gas ratios vs. decreased RBC-to-tissue ratios vs. both decreased), the decrease of gas uptake appeared to be mostly correlated with emphysematous tissue destruction or enlargement of distal airways as reflected by Xe129 ADC, and not the airflow obstruction as detected by Xe129 ventilation imaging or spirometry (except FEV_1/FVC). Varied patterns of abnormality in dissolved phase imaging were observed that could be related to different COPD phenotypes or stages of disease.

References: [1] Agusti AG. Respir Med, 2005. [2] Qing K, et al. J. Magn. Reson. Imaging, 2014. [3] Tsao J, et al. Magn.Reson. Med, 2013. [4] Tustison NJ, et al. J. Magn. Reson. Imaging, 2011. **Acknowledgement:** Supported by NIH grants R01 HL109618 and R44 HL087550, and Siemens Medical Solutions