Regional Mapping of Gas Uptake by Red Blood Cells and Tissue in the Human Lung using Hyperpolarized Xenon-129 MRI

Kun Qing[1], Kai Ruppert[2], Yun Jiang[3], Jaime F. Mata[2], Grady W. Miller[2], Yun Michael Shim[4], Chengbo Wang[2], Iulian C. Ruset[5,6], F. William Hersman[5,6], Talissa A. Altes[2], and John P. Mugler, III[1,2]

[1]Biomedical Engineering, University of Virginia, Charlottesville, VA, United States, [2]Radiology and Medical Imaging, University of Virginia, Charlottesville, VA, United States, [3]Biomedical Engineering, Case Western Reserve University, Cleveland, OH, United States, [4]Medicine, Pulmonary and Critical Care, University of Virginia School of Medicine, Charlottesville, VA, United States, [5]Xemed LLC, Durham, NH, United States, [6]Physics, University of New Hampshire, Durham, NH, United States

Introduction: The primary function of the lung is exchange of respiratory gases, which can vary substantially within the lung, especially for heterogeneous conditions such as chronic obstructive pulmonary disease (COPD). Nonetheless, there is currently no clinical imaging method that permits quantitative regional assessment of both gas delivery to the alveolar airspaces and gas uptake into the lung parenchyma and blood. Because xenon-129 (Xe129) dissolves in lung tissue and blood upon inhalation, hyperpolarized Xe129 MRI provides the opportunity to assess gas exchange and uptake in the lung [1-4]. The goal of this study was to (1) develop a robust approach based on Xe129 MRI for regional mapping of both ventilation (Xe129 in alveolar airspaces) and the fractions of Xe129 dissolved in lung parenchyma/plasma ("tissue") and red blood cells (RBCs) from multi-echo 3D data acquired in a single breath hold with a duration tolerable for subjects with lung disease, and (2) perform an exploratory study to characterize the associated signal fractions from tissue and RBCs in healthy subjects compared to those from subjects with COPD or asthma.

Methods: A multi-echo 3D radial pulse sequence was designed for acquiring dissolved- and gas-phase Xe129 images (Fig. 1). During each TR, three echoes (a half echo and two symmetric echoes) of dissolved-phase signals were acquired for calculation of tissue and RBC images, followed by two echoes of gas-phase data for calculation of ventilation images and a field map. Sequence parameters were: TR = 19 ms, TE1/TE2/TE3 = 0.74/2.36/3.98 ms (dissolved) and TE1/TE2 = 0.74/2.36 ms (gas), flip angle = 23° (dissolved) and 0.4° (gas), acquisition time = 11 s, and voxel volume = 7.6 x 7.6 x 17 mm³. A free-induction decay (FID) for dissolved-phase Xe129 was acquired at the end of the imaging acquisition to provide comparative whole-lung values for the RBC fraction. The Hierarchical IDEAL method [5] was used to separate the tissue and RBC components. MR studies were performed at 1.5T (Avanto; Siemens), using a flexible (Clinical MR Solutions) or rigid (custom built) Xe129 chest RF coil, under a physician's IND for hyperpolarized Xe129 MRI. Informed consent was obtained in all cases and a physician supervised each study. Enriched xenon gas (87% Xe129) was polarized using a prototype commercial system (XeBox-E10, Xemed). The study group included 5 healthy nonsmoking subjects (H1-H5, H3 imaged twice), 1 healthy subject who had smoked for 15 yrs (S1), 2 with smoking-related COPD (GOLD Stage III, S2 [imaged twice] and S3) and 2 asthmatics (A1 [imaged twice] and A2). Subjects inhaled ~1L of Xe129 mixed with N2 for a total volume equaling 1/3 of the subject's forced vital capacity as determined by spirometry. For quantitative comparison among subjects, slice-by-slice and whole-lung values of four ratios (total dissolved-phase to gas, tissue-to-gas, RBC-to-gas and RBC-to-tissue) were calculated for the ventilated region of the lung.
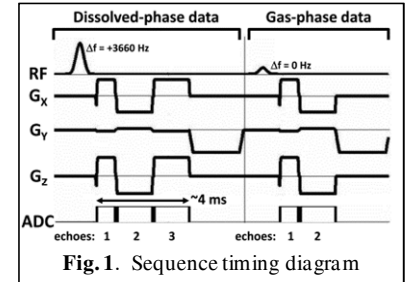

Fig.1. Sequence timing diagram

Results: Healthy subjects H1-H4 (ages 18-21) demonstrated generally uniform distributions of gas-phase, tissue and RBC signal intensities within each coronal image; Fig. 2a shows example images from H3. Healthy subject H5 (age 54) had several ventilation defects. Slice-by-slice and whole lung (Fig. 3) values for all ratios (except RBC-to-tissue ratios for subject H2) were similar among healthy subjects H1-H4, while values for subject H5 were generally lower. Tissue and RBC signal intensities, and total dissolved-phase to gas, tissue-to-gas, and RBC-to-gas ratios showed the general trend of increasing values from anterior to posterior due to the well-documented tissue compression in dependent areas of the lung [4], while the RBC-to-tissue ratio was generally flatter from anterior to posterior (Fig. 2d). Values for the total dissolved-phase to gas, tissue-to-gas, and RBC-to-gas ratios for smokers were mostly lower than those for healthy subjects (Fig. 3). Compared to COPD, the healthy smoker (S1) had higher values for 3 of the 4 ratios, and RBC-to-tissue ratios even higher than median values for healthy subjects. In contrast, subject S2 showed much lower ratio values and ratio maps that were very inhomogeneous (Fig. 2e). The two asthmatics were quite different in age (A1, 53 years; A2, 16 years), and, except for RBC-to-gas ratios, the results from the two asthmatics were markedly different (Fig. 2f). Subject A1 showed higher values for total dissolved-phase to gas and tissue-to-gas ratios, but much lower values for RBC-to-tissue ratios (Fig. 3). The ratio values for both asthmatics were lower than those for healthy subjects (Fig.3), with the exception of the RBC-to-tissue ratios for subject A2, which were higher than those for all other subjects. Subject A2 showed relatively uniform tissue-to-gas ratios, while subject A1 had elevated values in both apices in conjunction with reduced RBC-to-gas ratios (Fig.2f). Whole-lung mean values for the ratios of total dissolved-phase signal to gas, tissue-to-gas and RBC-to-gas for healthy subjects were significantly larger than those for the disease group (smokers and asthmatics, $p < 0.01$ for all ratios). RBC fractions from FID data were consistent with those from imaging data (mean absolute difference 1.6%). Percent differences between repeated acquisitions for the four ratios, averaged over the 3 subjects with repeat studies, were approximately 10% or less.

Conclusion: We have demonstrated an imaging method that permits regional mapping of the tissue and RBC fractions of Xe129 dissolved in the human lung, as well as quantitative comparison of tissue- and RBC-based ratios among subjects. The 11-sec breath-hold acquisition was well tolerated by both healthy volunteers and subjects with obstructive lung disease. Our preliminary results, although obtained from a small number of subjects in this exploratory study, suggest marked differences in the spatial distributions of Xe129 dissolved in tissue and RBCs among healthy subjects, smokers (including those with COPD), and asthmatics.

References: 1. Driehuys B, et al. Proc Natl Acad Sci USA 2006;103:18278-18283. 2. Abdeen N, et al. Magn Reson Med 2006;56:255-264. 3. Patz S, et al. Eur J Radiol 2007;64:335-344. 4. Cleveland ZI, et al. PLoS ONE 2010;5(8):e12192. 5. Tsao J, Jiang Y. Magn Reson Med 2012. doi: 10.1002/mrm.24441.
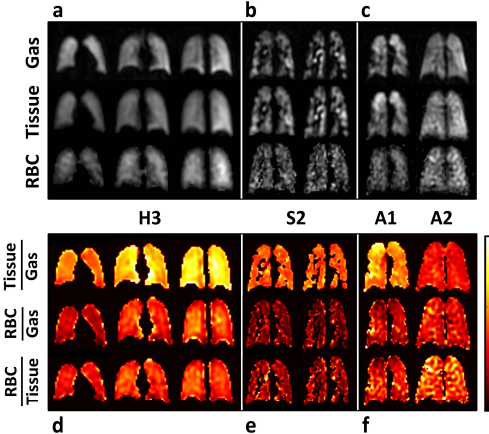
Fig. 2 (left). **(a-c)** Coronal gas, tissue and RBC images, and **(d-f)** corresponding tissue-to-gas, RBC-to-gas and RBC-to-tissue ratio maps. The color scale maximum is 1.0 for tissue-to-gas maps, 0.5 for RBC-to-gas maps and 0.7 for RBC-to-tissue maps (except1.0 for asthmatic A2).

Fig. 3 (right). Whole-lung ratio values (mean ± SD) for all subjects. * marks values for repeated acquisitions.