

Assessment of Cystic Fibrosis in Pediatric Subjects using Hyperpolarized Xenon-129 MRI: Regional Mapping of Gas Uptake by Lung Tissue and Blood

Kun Qing¹, Kai Ruppert^{1,2}, Tally A. Altes¹, G. Wilson Miller¹, Yun Jiang³, Jaime F. Mata¹, Yun M. Shim¹, Chengbo Wang¹, Steven Guan¹, Julian C. Ruset^{4,5}, F. William Hersman^{4,5}, and John P. Mugler¹

¹University of Virginia, Charlottesville, VA, United States, ²Cincinnati Children's Hospital, Cincinnati, OH, United States, ³Case Western Reserve University, Cleveland, OH, United States, ⁴Xemed LLC, Durham, NH, United States, ⁵University of New Hampshire, Durham, NH, United States

Target audience: Physicians and scientists interested in functional lung imaging and cystic fibrosis.

Introduction: Cystic fibrosis (CF) is characterized by thick mucus in the airways resulting in persistent pulmonary infection and inflammation, which contribute to progressive tissue changes and decreasing lung function¹. Early treatment for CF can improve quality of life and increase lifespan. Three-dimensional Xe129 dissolved-phase imaging² provides a new method to evaluate the primary function of the lung -- gas exchange -- by directly mapping gas uptake by tissue and blood. As a non-invasive MR imaging method, it is particularly suited to monitoring functional changes of the lung and evaluating treatment efficacy for CF subjects, especially those in the pediatric population. In this study, we investigated functional changes in the lung for pediatric subjects with CF, as compared with healthy subjects.

Methods: Five CF subjects (age 14 \pm 2.8 yrs, FEV₁%pred 62% \pm 9%, FEV₁/FVC 0.76 \pm 0.12) and 7 young healthy subjects (age 19 \pm 2 yrs, FEV₁%pred 101% \pm 10%, FEV₁/FVC 0.83 \pm 0.06) underwent 3D Xe129 dissolved-phase imaging. 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 \sim 10 s, and voxel volume 7.6 x 7.6 x 17 mm³. The Hierarchical IDEAL method³ was used to separate the tissue (lung parenchyma and plasma) and red blood cell (RBC) components from the multi-echo dissolved-phase images. For quantitatively analyzing lung function, four ratios were calculated: total dissolved-phase-to-gas, tissue-to-gas, RBC-to-gas and RBC-to-tissue (the latter three shown as maps). In five CF subjects, high-resolution 3D proton images were also acquired using a 3D spoke-radial, balanced SSFP pulse sequence with parameters: TR 1.26 ms, TE 0.09 ms, flip angle 13° (nonselective), and isotropic 1.7-mm resolution. 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. Informed consent was obtained in all cases. Enriched xenon gas (87% Xe129) was polarized using a prototype commercial system (XeBox-E10, Xemed).

Results: Healthy subjects showed generally homogeneous signal distribution in all images, and ratios which were relatively consistent among subjects: total dissolved-phase-to-gas: 1.41% \pm 0.09% (mean \pm standard deviation), tissue-to-gas: 1.17% \pm 0.12%, RBC-to-gas: 0.35% \pm 0.03%, and RBC-to-tissue: 0.30 \pm 0.03 (Fig.1).

All CF subjects showed numerous ventilation defects, especially in the right upper lobe. Three CF subjects had elevated mean tissue-to-gas ratios (1.4%, 1.5% and 2.8%, Fig. 1) compared with the healthy group. This could come from accumulated mucus in the airways and/or lung parenchymal inflammation. The other 2 CF subjects had lower mean tissue-to-gas ratios (0.9%, 1.0%), which could be associated with tissue destruction or hyperexpansion. All tissue-to-gas ratio maps were inhomogeneous (examples shown in Fig. 2). Interestingly, for all CF subjects imaged, the average tissue-to-gas ratios were higher in the right lung than the left lung (Fig. 2, Fig. 3), and most showed lower tissue-to-gas ratios in the right upper lobe as compared to the other lobes in the right lung (Fig. 2, arrows), which suggests tissue destruction in the right upper lobe. In more severe cases, such as C4, the high resolution proton images showed prominent bronchiectasis and mucus plugging in the right upper lobe (Fig. 4). These observations are consistent with previous evidence that initial pulmonary involvement in cystic fibrosis is often in the upper lobes, with disease progression spreading to other regions.

In contrast to tissue-to-gas ratio maps, RBC-to-tissue ratio maps were generally homogeneous for the CF subjects, and the mean RBC-to-tissue ratios were in the normal range or slightly higher than the mean for the healthy group. Considering the accumulated mucus in the airways, which should in principle impede gas transfer to the RBCs and thus decrease the RBC-to-tissue ratios, the normal or nearly normal RBC-to-tissue ratios might come from increased angiogenesis in CF⁴ due to inflammation and/or other compensatory mechanisms to preserve gas exchange. For example, for C5 (Fig. 1), the tissue-to-gas and RBC-to-gas ratios (2.8% and 0.86%) were both two-fold larger than the corresponding mean ratios for healthy subjects (1.2% and 0.35%). The overall gas uptake to the RBCs (RBC-to-gas ratios) for the CF subjects was similar to or higher than value for the healthy group (Fig. 1).

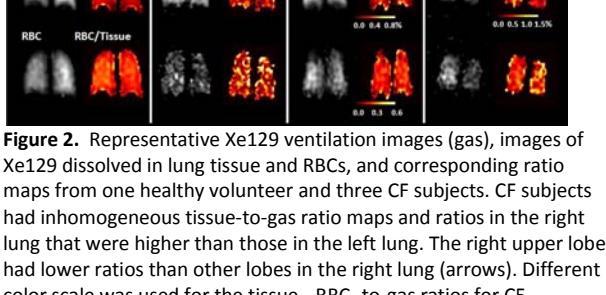


Figure 2. Representative Xe129 ventilation images (gas), images of Xe129 dissolved in lung tissue and RBCs, and corresponding ratio maps from one healthy volunteer and three CF subjects. CF subjects had inhomogeneous tissue-to-gas ratio maps and ratios in the right lung that were higher than those in the left lung. The right upper lobe had lower ratios than other lobes in the right lung (arrows). Different color scale was used for the tissue-, RBC- to-gas ratios for C5.

Conclusion: Xe129 dissolved-phase imaging shows high potential for regionally characterizing functional changes in gas exchange of the lung in the early stages of cystic fibrosis.

References: [1] Meyer KC, et al. Am J Respir Crit Care Med. 1997 Nov;156(5):1536-40. [2] Qing K, et al. J. Magn. Reson. Imaging. doi: 10.1002/jmri.24181. [3] Tsao J, et al. Magn. Reson. Med., 70: 155-159. doi: 10.1002/mrm.24441. [4] Susanna A, et al. Am J Respir Crit Care Med. 2000 Jun;161(6):1877-80

Acknowledgement: Supported by NIH grants R43 HL108452 and RO1 HL109618, and Siemens Medical Solutions

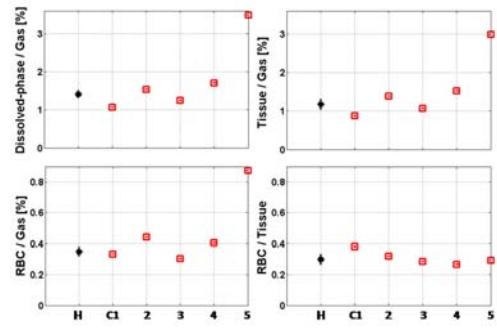


Figure 1. Whole-lung ratio values for all healthy subjects (mean and standard deviation plotted on the left in black) and the 5 CF subjects.

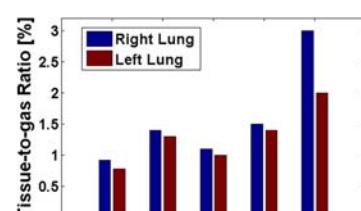


Figure 3. Mean tissue-to-gas ratios of the right lung were higher than those for the left lung in all CF subjects.

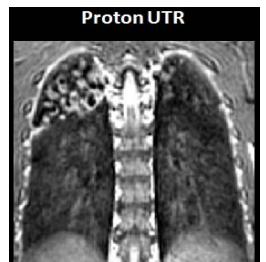


Figure 4. Proton UTR/UTE images acquired in C4.