Validation of ^{129}Xe diffusion MRI as a measure of airspace enlargement in human lungs

Robert Paul Thomen[1,2], James D Quirk[3], David Roach[1], Tiffany Egan-Rojas[1], Kai Ruppert[1], Iulian Ruset[4], Talissa Altes[5], Dmitriy Yablonskiy[3], and Jason C Woods[1,2]
[1]Center for Pulmonary Imaging, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States, [2]Physics, Washington University in St Louis, St Louis, MO, United States, [3]School of Medicine, Washington University in St Louis, St Louis, MO, United States, [4]XeMed, LLC, Durham, NH, United States, [5]Radiology, University of Virginia Hospital Medical Center, VA, United States

Purpose:

^{3}He diffusion MRI has been shown to be highly sensitive to the micro-geometry of acinar ducts and alveoli [1,2] and has demonstrated particular merit in quantitative assessment of heterogeneous emphysema in human subjects [3]. However, the high cost of ^{3}He has shifted focus toward ^{129}Xe, despite its lower gamma and lower achievable polarization. The quality and SNR of ^{129}Xe MRI has increased in recent years [4,5] and apparent diffusion coefficient (ADC) increases have been seen in COPD subjects compared to controls [6]. This is promising, but its utility in probing pulmonary microstructure requires validation since it possesses a much smaller diffusion coefficient (in the dilute limit in air, D_0 = 0.14 cm^2/s compared to helium D_0 = 0.86 cm^2/s) and has the unique ability to perfuse into the lung tissue and blood [7-9]. Here we present the first direct comparisons of ^{129}Xe diffusion MRI to quantitative histology in human lungs, in order to validate the imaging technique as a biomarker for airspace enlargement in COPD and take steps toward regulatory advancement.

Methods:

The left lungs from 5 severe COPD and 2 IPF patients were removed during lung transplantation. These IPF lungs here serve as controls since they have little to no airspace enlargement. After explantation (and plural surface repair where necessary) the *ex-vivo* lungs were purged of oxygen with multiple washouts of nitrogen before a 50/50 ^{129}Xe/N_2 mixture was introduced (P ≈ 24% using a XeMed polarizer). Lungs were imaged at inflation on a 1.5T Siemens Avanto (Siemens, Erlanger, Germany) using a diffusion-weighted 2D-multislice FLASH sequence (TR/TE=22/16ms, FA=5°, matrix size =30x64, Voxel Size ≈7x7x30 mm^3, b values = 0, 12.5 s/cm^2, Δ = δ = 5 ms, rise time = 0.4 ms). The lung was then inflated to a constant pressure of 10" H_20 and slowly frozen over liquid nitrogen at around 77-90 K. The frozen inflated lung was then cut into 1 cm thick axial slices; small cylindrical samples were taken for histological staining, microscopic imaging, and morphological analysis. The mean linear intercept (L_m) was measured for all samples via point and intercept counts, and the surface area to volume ratio (SA/V) calculated by SA/V = 4/L_m [1]. Care was taken to ensure the locations of the tissue samples were accurately matched to image slices for proper comparison of ADC with L_m and SA/V.

Results and Discussion:

Average ADC values for the COPD lungs were around 2x higher than in the control lungs (0.07 cm^2/s for COPD, 0.03 cm^2/s for control, $p < 10^{-4}$). The average L_m in COPD lungs was 0.072 cm (SA/V = 55.6 cm) while the average L_m in the control lungs was 0.034 cm (SA/V = 117.6 cm) (IPF/COPD p-value = 0.009). While these COPD lungs had severe, somewhat homogeneous destruction, higher ADC correlated with larger L_m as shown in Figure 1 (r=0.85, Pearson correlation) and thus smaller SA/V. Figure 2 presents ADC maps of representative COPD and control lungs, corresponding lung slices with sampled tissue locations, and histological photomicrographs of the indicated samples.

Conclusions:

Our results provide direct evidence that ^{129}Xe diffusion MRI correlates with alveolar enlargement in COPD in human lungs. We anticipate that the results can further the regulatory advancement of ^{129}Xe as a diagnostic contrast agent in pulmonary MRI.

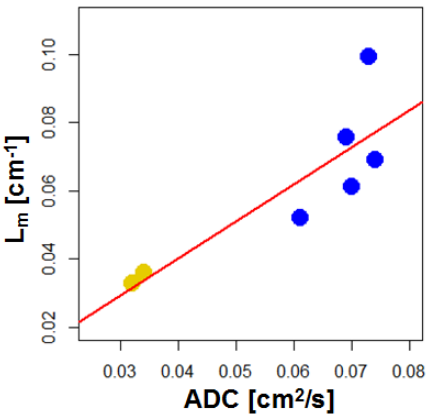

Figure 1

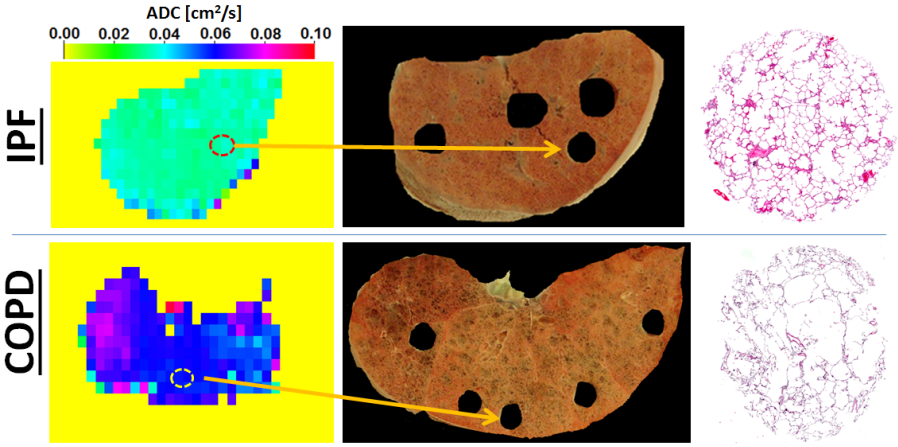

Figure 2

References:

[1] Yablonskiy *et al., J Appl Phisiol* 107:1258 (2009) [2] Quirk *et al., Radiology* 260: 866 (2011). [3] Woods *et al., Magn Reson Med* 56:1293 (2006). [4] Hersman *et al. Phys Rev Lett.* 96:5 (2006). [5] Svenningsen *et al., J Magn Reson Imaging* 38:6 (2013). [6] Ouriadov *et al., Magn Reson Med* 70:1699 (2013). [7] Patz *et al., Eur J Radiol* 64:335-44 (2007). [8]Qing *et al., NMR Biomed* (2014). [9] Möller *et al. Magn Reson Med.* 47:1029-51 (2002)