Evaluation of Emphysema Severity and Progression in a Rabbit Model: A Comparison of Hyperpolarized He-3 and Xe-129 ADC with Morphometry

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Introduction: Hyperpolarized helium-3 (He-3) diffusion MR has been evaluated in animal models and humans with emphysema [1-5], and it is thought to provide information about the morphology of the lung microstructure. In animal models of emphysema, the post-mortem He-3 Apparent Diffusion Coefficient (ADC) has been shown to be correlated with the alveolar internal area and mean linear intercept [5], and in patients with emphysema, a correlation between the He-3 ADC and clinical measures of disease severity has been found [2]. To our knowledge similar studies have not been reported with hyperpolarized xenon-129 (Xe-129). In this study, He-3 and Xe-129 ADC values were measured in the lungs of rabbits with induced emphysema during 8 weeks following elastase administration. Histology and morphometry of the lungs were performed at the end of the 8-week period and correlated with the in-vivo ADC values.

Methods and Materials: Nine New Zealand rabbits (4.5–6.0 kg) received a single endotracheal instillation above the carina with a high-pressure microsprayer (PennCentury, PA), guided by fluoroscopy. Three were instilled with 30 units of porcine elastase diluted with saline (moderate group); three received 5 units of diluted elastase (mild group) and three were instilled with saline only (control group). All animals were anesthetized with a mixture of Xylazine/Ketamine and intubated with an endotracheal tube before being imaged at baseline and re-imaged at 2, 4, 6 and 8 weeks following instillation. Imaging was done during a breath-hold following the administration of 50 cc of He-3 (polarization: 30-38%) or 50 cc of Xe-129 (polarization: 10-15%)(IGI9600 polarizer, MITI), corresponding to lung pressures of 20-25 cm H_2O. MRI was performed on a 1.5 Tesla whole-body MR scanner (Sonata, Siemens) using RF coils tuned to the He-3 and Xe-129 resonant frequencies. FLASH-based sequences with bipolar gradients for diffusion sensitization were used. Since the diffusivity of Xe-129 in air is several times slower than that for He-3 in air, we used higher b values for Xe-129. To achieve these higher b values, and since γ for Xe-129 is 3 times lower than that for He-3, the diffusion time for Xe-129 was longer than that for He-3. The b values were: b=0, 1.6 s/cm^2 or b=0, 4 s/cm^2 for He-3; b=0, 5 s/cm^2 or b=0, 10 s/cm^2 for Xe-129. (In the results, b_H refers to the non-zero b value for each pair). Contiguous image slices were acquired with: matrix size, 64x128; in-plane resolution, 2.2x2.2mm^2 (He-3) or 2.7x2.7mm^2 (Xe-129); TR/TE, 12/6.8ms (He-3) or 16/11ms (Xe-129). At 8 weeks following instillation, all animals were euthanized and their lungs fixed and prepared for histology. Morphometry of multiple tissue samples per animal/lung was performed according to the method described by Lum [6]. The alveolar Mean Chord Length (MCL) values were measured and correlated with the He-3 and Xe-129 in-vivo ADC values obtained at the week-8 imaging session.

Results: At week 2 post-instillation, the moderate emphysema group showed mean He-3 ADC increases of 17.8% and16.0% for b_H=1.6 and 4 s/cm^2, respectively, and mean Xe-129 ADC increases of 1.4% and 3.9% for b_H= 5 and 10 s/cm^2, respectively. The mild group increased 10.8% and 4.8% for He-3 (b_H= 1.6 and 4 s/cm^2, respectively), while for Xe-129 the increases were 0.7% and 3.4% (b_H= 5 and 10 s/cm^2, respectively). The control group had an ADC decrease for all b-values, with -4.0% and –5.0% for He-3 (b_H= 1.6 and 4 s/cm^2, respectively), and –2.8% and –0.9% for Xe-129 (b_H=5 and 10 s/cm^2, respectively). From week 2 to week 8, He-3 ADC values remained constant or showed a slight tendency to decrease while the Xe-129 ADC values increased. Figure 1 shows He-3 and Xe-129 ADC maps from the same rabbit with moderate emphysema at three different time points, as well as the corresponding mean $\pm$ std and histograms from the entire set of images. After week 2 post-elastase, the ADC increase in the He-3 maps and histograms is clearly seen. After histology/morphometry, the individual He-3 and Xe-129 ADCs from each animal at 8 weeks following instillation were correlated with the average MCL of all tissue samples from each respective rabbit. The highest correlations were obtained for He-3 ADC measurements, with r=0.846 (p<0.001) for b_H = 1.6 s/cm^2 (Figure 2) and r=0.844 (p<0.001) for b_H = 4 s/cm^2. The correlation for Xe-129 ADC measurements with b_H = 5s/cm^2 was similar with r=0.780 (p<0.001), while r=0.741 (p<0.001) for b_H = 10 s/cm^2 (Figure 2).

Discussion: Our in-vivo study confirms prior work done in postmortem animals, demonstrating a high correlation between the He-3 ADC and distal airspace size as measured by lung histology. Despite lower polarizations, nearly as high correlations were found for the Xe-129 ADC and lung histology. From our results, the sensitivity of the Xe-129 ADC appeared to be less than that of the He-3 ADC to developing emphysema. In order to fairly compare the two gases we increased the diffusion time for the Xe-129 but it is possible that the slower diffusion rate of Xe-129 requires even longer diffusion times to be optimally sensitive to changes in the lung microstructure.

References:
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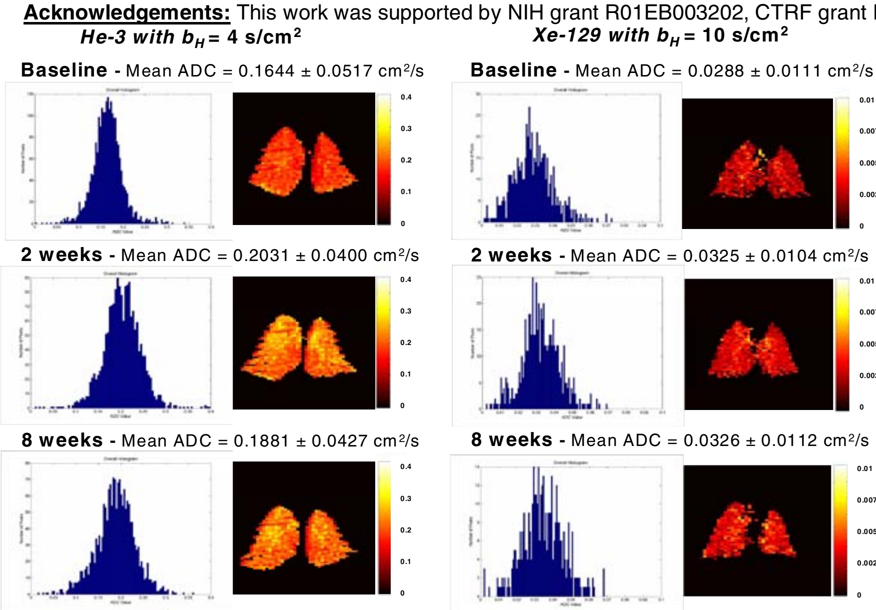

Figure 1 - ADC maps of the most posterior slice and overall histograms from the same animal (moderate emphysema with largest ADC increases) imaged at 3 different time points, with He-3 (left), b_H=4 s/cm^2, and Xe-129 (right), b_H=10 s/cm^2. The histograms represent the ADC values for all of the images acquired in the respective scan.

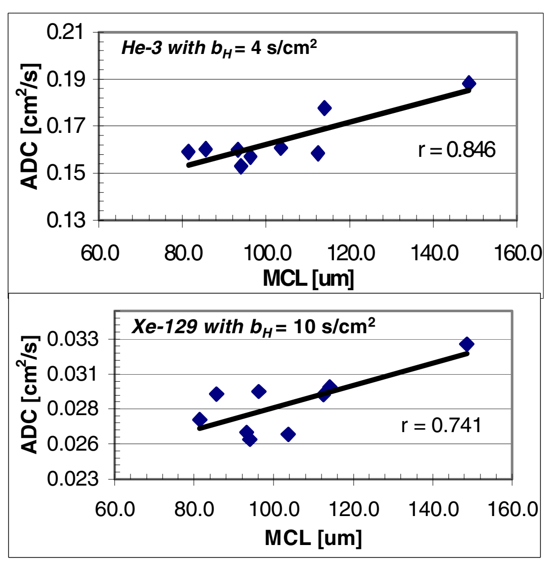

Figure 2 – Correlation plots between Mean Chord Length (MCL in µm) and He-3 ADC with b_H=4 s/cm^2 (top) or Xe-129 ADC with b_H=10 s/cm^2 (bottom).