

Hyperpolarized He-3 ADC in a Rabbit Model of Emphysema: Evaluation of Progression and Sensitivity in an 8-Week Study

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Introduction: The Apparent Diffusion Coefficient (ADC) of hyperpolarized (hp) Helium-3 (He-3) has been evaluated in animal models and humans with emphysema [1-5], but to our knowledge evaluation of the temporal evolution of emphysema with the ADC has not been reported. In this study we quantified the early changes of emphysema with He-3 ADC in a rabbit model and followed the progression throughout the first two months following elastase induction of emphysema. We also investigated the relative sensitivity of different b-values for the detection of early emphysema.

Methods and Materials: Six New Zealand rabbits (3.5 - 4.5 kg) were anesthetized with a mixture of Xylazine/Ketamine and intubated with an endotracheal tube. The animals were imaged during a breath-hold following the inhalation of 50cc of hp He-3 (polarization: 30-36% using a IGI9600 polarizer, MITI, Durham, NC). Each animal was imaged at baseline and re-imaged in intervals of 2 to 4 weeks for 8 weeks following the administration of elastase. In five rabbits, a single injection of a mixture of pancreatic porcine elastase and saline was administered above the carina via a microsyringe (PennCentury, Philadelphia, PA). One of the rabbits received the same amount of elastase mixture in the right main bronchus. All elastase injections were guided by fluoroscopy. Imaging was performed on a 1.5 Tesla whole-body MR scanner (Magnetom Sonata, Siemens, Malvern, PA) using RF coils tuned to the He-3 resonant frequency. Two FLASH-based diffusion-weighted sequences with bipolar gradients and different b-values were used (b = 0, 1.6 s/cm² and b = 0, 4 s/cm²). Four to six contiguous image slices with 10-13 mm thickness were acquired with matrix size = 64x128 and in-plane resolution = 2.2x2.2 mm². For each rabbit, the mean and standard deviation of ADC values were computed for each sequence and time point. The mean and standard deviation of ADC values for all 6 rabbits were also calculated for each sequence and time point.

Results: The means and standard deviations of ADC values for all rabbits at each time point are presented in figures 1 and 2. The percent change relative to each preceding time point (fig. 2) shows the greatest increase in ADC values occur during the first two weeks followed by a decreasing rate of change on subsequent time points with an increase of 14.7% and 10.4% in the first 2 weeks for b = 0, 4 s/cm² and b = 0, 1.6 s/cm², respectively (p<0.0002). For b = 0, 4 s/cm², the cumulative change was 24.6% after 4 weeks and 30.5% after 8 weeks compared with 13.5% at 4 weeks (p<0.0005) and 17.7% at 8 weeks (p<0.0112) for the b=0, 1.6 s/cm². Figures 3A,B and C are from a single rabbit and show the overall histogram and selected ADC maps (b=0, 4 s/cm²) for the rabbit with the injection in the right main bronchus. Relative to baseline, elevated ADC values are seen in the right lung and, to a lesser extent, in the left lung, and both lungs become hyper-expanded following elastase administration.

Discussion: Our measurements suggest that the diffusion pair b=0, 4 s/cm² is more sensitive than b=0, 1.6 s/cm² to small changes in the lung microstructure when the underlying alveolar structure is the size of the rabbit. The normal rabbit alveoli (~150 μm in diameter [6]) are smaller than normal adult human alveoli (~200-300 μm in diameter [7,8]). In [4], the b values of 0, 1.6 s/cm² were selected to be sensitive to changes of moderate to severe emphysema in the adult human lung in which the alveoli are much larger than those in this study. Our results suggest that further investigation is warranted into the relationship between the b values used to measure hp He-3 ADC, the underlying size and morphology of the distal airspaces being evaluated, and the ADC that is obtained. Histology is currently being performed for validation of our results.

- References:**
1. Saam BT et al. Magn. Reson. Med. 2000; 44:174-179.
 2. Yablonskiy DA et al. PNAS 2002, 99(5); 3111-3116.
 3. Woods JC et al. Magn. Reson. Med. 2004; 51:1002-1008.
 4. Salerno et al. Radiology 2002; 222:252-260.
 5. Chen XJ et al. Magn. Reson. Med. 2000; 42:721-728.
 6. Kovar J, Sly P, Willet K. J Appl Physiol 2002; 93:629-635.
 7. West J. Respiratory Physiology, the essentials, 4, 6th ed, 1999.
 8. Hansen J, Ampaya E. J Appl Physiol 1975; 38:990-995.

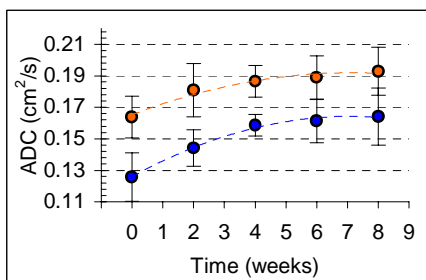


Figure 1 – In orange values for b=0, 1.6 and in blue values for b=0, 4 s/cm². Lines represent the trend for each set of points.

	b1.6: baseline	b1.6: 2 weeks	b1.6: 4 weeks	b1.6: 6 weeks	b1.6: 8 weeks	Total
Mean [cm ² /s]	0.164±0.0132	0.181±0.0169	0.186±0.0101	0.189±0.0138	0.193±0.0152	
Percent change	0.0%	10.4%	3.1%	1.3%	2.1%	17.7%
	b4: baseline	b4: 2 weeks	b4: 4 weeks	b4: 6 weeks	b4: 8 weeks	Total
Mean [cm ² /s]	0.126±0.0154	0.144±0.0116	0.158±0.0068	0.161±0.0138	0.164±0.0181	
Percent change	0.0%	14.7%	9.9%	1.9%	1.7%	30.5%
P (b1.6 vs b4)	<0.0001	<0.0002	<0.0005	<0.0001	<0.0112	

Figure 2 – Mean ADC values ± standard deviation and percent changes of the mean values for all of the rabbits at each time point.

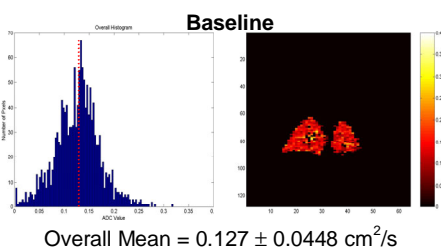


Figure 3A - Overall histogram and mean value (marked in red) at baseline (b=0, 4 s/cm²). ADC map (right) shows both lungs with homogeneous ADC values.

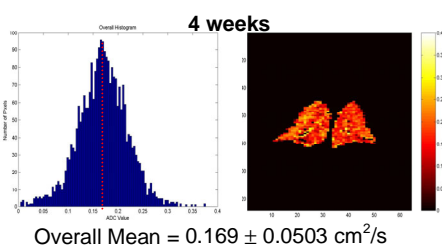


Figure 3B - Overall histogram and mean value at 4 weeks. ADC map (right) shows right lung (left in the figure) with slightly elevated ADC values.

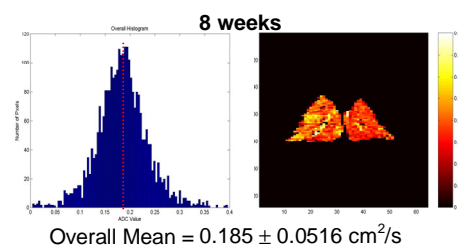


Figure 3C - Overall histogram and mean value at 8 weeks. ADC map (right) shows right lung (left in the fig.) with highly elevated ADC values.