Mapping of ³He Apparent Diffusion Coefficient Anisotropy at Sub-Millisecond Diffusion Times in Sham-Instilled and Elastase-Instilled Rat Lungs

X. Xu[1,2], J. Parra-Robles[3], A. Ouriadov[1], and G. E. Santyr[1,4]

[1]Imaging Laboratories, Robarts Research Institute, London, Ontario, Canada, [2]Department of Physics, University of Western Ontario, London, Ontario, Canada, [3]University of Sheffield, Sheffield, United Kingdom, [4]Department of Medical Biophysics, University of Western Ontario, London, Ontario, Canada

Introduction: Perhaps one of the most unique implementations of hyperpolarized ³He is diffusion-weighted MR imaging, taking advantage of the much larger apparent diffusion coefficient (ADC) of ³He (˙0.2 cm²/s), compared to ¹H (1.1 x 10⁻⁵ cm²/s). ³He diffusion in the lungs is restricted by airway and alveoli walls and therefore is highly dependent on lung microstructure. ³He ADC has been shown to be sensitive to changes in terminal airway anatomy, specifically alveolar damage due to emphysema in both humans [1] and animal models [2]. At the terminal airway, ³He diffusion has been demonstrated to be anisotropic [3], described by two components: (i) a longitudinal diffusion coefficient (D_L), reflective of diffusion along the length of the duct, and (ii) a transverse diffusion coefficient (D_T), reflective of diffusion perpendicular to the duct. D_L measured at a diffusion time of 1.8 ms has been previously shown to reflect emphysema in humans [3]. At shorter diffusion times (< 1 ms), it is anticipated that D_T will be sensitive to changes at the alveolar wall and therefore may be a more sensitive parameter for probing the changes associated with emphysema, The purpose of this work was to measure and compare D_L and D_T maps in sham-instilled and elastase-instilled Wistar rats at two sub-millisecond (360 µs and 800 µs).

Methods: *All experiments were performed following a University of Western Ontario Council on Animal Care approved protocol.* Four healthy Wistar rats (213±46g) were instilled with 70IU of elastase and three were sham-instilled with 0.4mL of saline [2]. MR imaging was performed between six to eight weeks post instillation at 3T using a custom-built high performance insert gradient (50 G/cm, maximum slew rate of 4000T/m/s) [4]. Hyperpolarized ³He was obtained from a turn-key polarizer (Helispin, GEHC) and administered to the rats using a custom ventilator system [5]. A 2-D gradient echo sequence incorporating diffusion-sensitization gradients was used to image each rat at diffusion times of 360 µs and 800 µs. At each diffusion time, eight images were obtained corresponding to diffusion-sensitization gradient strengths between 1 G/cm and 30 G/cm, providing b values ranging between 1 s/cm² and 100 s/cm². D_L and D_T maps were calculated by fitting a multi-component function [3 (equations [5][6])] to the data as a function of b. Following imaging, the rats were euthanized and lungs were extracted and fixed under inflation at the end of each experiment for histological measurement of mean linear intercept.

Results and Discussion: An increase of mean linear intercept, L_m, of 70% from 85 µm to 145 µm on average was observed, consistent with expected elastase damage [2]. Table 1 shows the mean D_T, D_L measurd in both cohorts, as well as the p-values from a paired T-test. Although D_L appears to be more sensitive than D_T for detecting emphysema at the longer diffusion time (800 µs) as suggested previously [3], D_T measured at the shorter diffusion time (360 µs) shows more significant changes overall. To the extent that elastase damage represents emphysema, these results suggest that if multiple, strong b values (up to ~4 s/cm²) can be achieve clinically for ³He at sub-millisecond diffusion times, mapping of D_T may be helpful for earlier diagnosis of emphysema in human subjects. Alternatively, ¹²⁹Xe or mixtures of ³He with heavier gases may be useful for extending sensitivity of D_T to longer diffusion times.

	D_T (δ =360µs)	D_L (δ=360µs)	D_T (δ=800µs)	D_L (δ=800µs)
Sham-instilled	0.0567	0.277	0.025	0.54
Elastase-instilled	0.14	0.247	0.028	0.70
p-value	0.00195**	0.4674	0.5739	0.00933*

Table 1. Mean D_T and D_L values in cm²/s and statistical differences.

References:
[1] J. C. Woods et al., MRM.2006; 56:1293-1300
[2] G. Peces-Barba et al., ERJ. 2003; 22:14-19
[3] D. A. Yablonskiy et al., PNAS. 2002; 99:3111- 3116
[4] P. Foster-Gareau et al., MRM. 2003; 49: 5: 968-971.
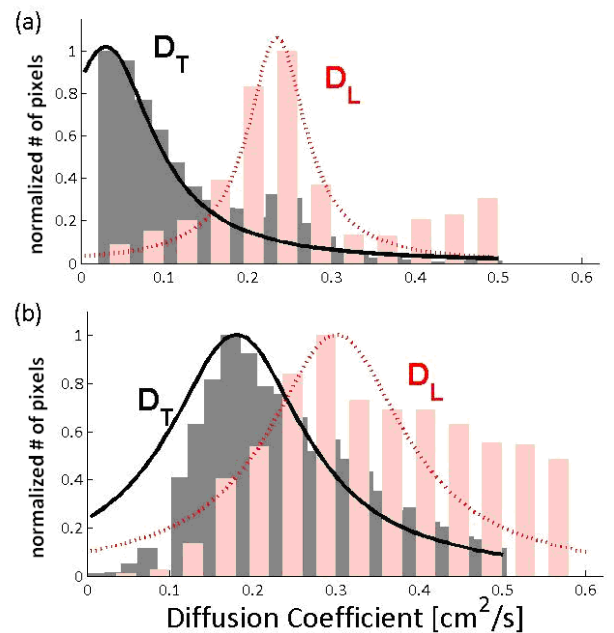[5] G. E. Santyr et al., MRM. 2008;

Figure 1. Transverse (D_T) and longitudinal (D_L) diffusion coefficient histograms for representative (a) sham-instilled and (b) elastase-instilled rats