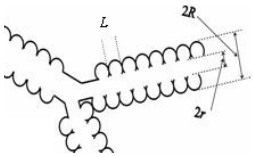
In vivo Lung Morphometry Identifies Detail Changes of Lung Microstructure with Emphysema Progression

D. A. Yablonskiy[1], A. L. Sukstanskii[1], J. C. Woods[2], A. J. Bierhals[1], Y. V. Chang[2], R. E. Jacob[2], M. S. Conradi[2], and D. S. Gierada[1]

[1]Mallinckrodt Institute of Radiology, St. Louis, MO, United States, [2]Department of Physics, Washington University

Introduction: Numerous measurements of hyperpolarized ^{3}He gas ADC in human lungs indicated substantial differences between healthy and emphysematous lungs. While in healthy lungs ADC is about 0.2 cm^2/sec, in emphysema it can be as high as $D_0 = 0.88$ cm^2/s - free diffusion of ^{3}He gas in air. The *in vivo* lung morphometry technique (1, 2) has a potential for obtaining information on lung microstructure based on MRI measurement of diffusion of hyperpolarized ^{3}He gas. Herein we use this method to identify changes in lung microstructure at the initial stages of emphysema. While the original method (1) relied on collecting diffusion data with a fixed diffusion time and variable diffusion sensitizing gradient strength, here we explore another approach when data are collected with a fixed *b*-value and variable diffusion times.

Theory: According to the lung geometric model (3) adopted in (1, 2), an acinar airway is considered as a cylinder covered by a sleeve of alveoli (see Fig. 1). Diffusion of ^{3}He gas in each airway is anisotropic and described by distinct longitudinal and transverse diffusion coefficients, D_L and D_T. In the millisecond range of diffusion times, the parameters D_L and D_T are related to the geometrical parameters of acinar airways R, r, L by the following empirical expressions (2):



$$D_L = D_0 \cdot \left\{1-\left(R/L\right)^{1/2} \cdot \left[1-\exp\left(-2.5\cdot\left(1-r/R\right)^{1.8}\right)\right]\right\}, \quad D_T = 0.44\, D_0 \cdot \left(R/L_{diff}\right)^{4\cdot\left[1-\left(R/L_{diff}\right)^{0.7}\right]} \qquad [1]$$

Here $L_{diff} = \left(4D_0\Delta\right)^{1/2}$ is the characteristic free-diffusion length for two-dimensional diffusion. Equations [1] are valid for $R/L_{diff} < 0.7$ and diffusion time $\Delta < 12$ ms (time required for ^{3}He molecule to diffuse a distance of about 1 mm – an average acinar airway length). The important result in Eqs. [1] is independence of D_L on diffusion time. Since a multitude of uniformly oriented airways is present in each imaging voxel ADC has a simple relationship to D_L and D_T (1):

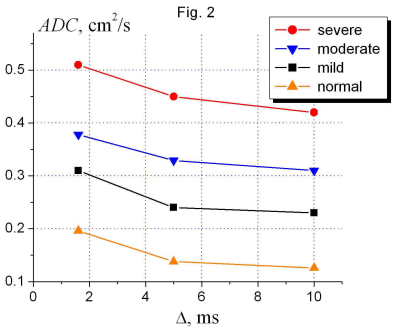
$$ADC = \left(D_L + 2D_T\right)/3 \qquad [2]$$

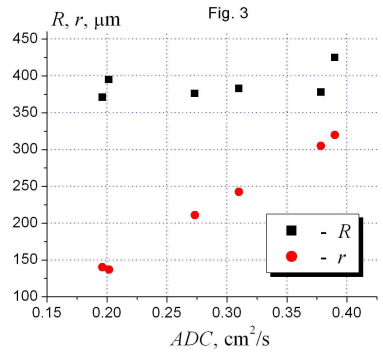
Equations [1,2] provide a platform for evaluating acinar airway geometric parameters by means of measuring *ADC* dependence on diffusion time.

Methods: As opposed to the typical *in vivo* use, hyperpolarized ^{3}He MR imaging in this study was performed *ex vivo* on the resected lung specimens. This insured distribution of the ^{3}He throughout all of the airspaces and allowed repeated measurements from a single bolus of gas. Lungs were obtained from lung transplant patients and unmatched donors, and lobes were obtained from surgery for lung cancer. All resected lobes and lungs were prepared for imaging by attaching tubing to inflate the specimen and sealing any air leaks. Ten specimens were studied. The ^{3}He gas was hyperpolarized by the spin-exchange technique using a custom-built polarizer or a commercial polarizer (General Electric Medical) to achieve polarization levels of approximately 40%. The lungs were purged of oxygen with pure nitrogen gas immediately prior to imaging. The polarized ^{3}He (approximately 400 ml) was mixed with nitrogen to a total gas volume of approximately 1 liter. The gas mixture was injected into the lungs or lobes to a pressure of 10-12 cm H_2O, gently withdrawn and re-injected to the same pressure two to three times to facilitate mixing throughout all of the airspaces, then re-injected to the same distending pressure immediately prior to starting the scan.

MR imaging was performed on a 1.5 Tesla MR scanner (Siemens Magnetom Vision) using a custom, lab-built, transmit-receive, single-turn solenoid coil tuned to the ^{3}He resonance frequency of 48.47 MHz. A set of 2D diffusion images covering the whole lung specimen with two b-values (0 and 1.38 sec/cm^2) was acquired for three diffusion times Δ of 1.6 ms, 5.0 ms, and 10.0 ms, and slice thicknesses of 10 mm. Other sequence parameters were: flip angle - 3-5°; in-plane resolution - 5.5 mm x 5.5 mm.

Results and Discussion: We found that in all cases *ADC* decreases with diffusion time increases. Four examples for normal lungs, lungs with mild, moderate and severe emphysema are shown in Fig. 2. We also found that the theoretical model in Eqs. [1,2] can describe the data only when *ADC* corresponding to Δ =1.6 ms is less than 0.4 cm^2/sec (healthy lungs, mild and moderate emphysema). This could be expected since in severe emphysema the geometrical model of acinar airways (Fig. 1) is no longer adequate due to alveolar wall destruction. Results of data analysis obtained from six data sets that satisfy this criterion are present in Fig. 3. The results demonstrate a very insightful picture of emphysema progression. The external airway radius, R, grows only slightly from normal lung value, meaning that at these stages (mild and moderate emphysema) lungs experience only very small increase in their volume. At the same time, the internal airway radius, r, grows dramatically from a value that is less than half of R in normal lungs to a value approaching R when emphysema advances to severe stage. This means that at the initial stages of emphysema, walls separating alveoli belonging to the same acinar airway are destroyed by the disease without substantial effect on inter-airway walls. This destruction gradually progresses with the disease progression and becomes global after r reaches R. For pulse sequence employed in this study, this corresponds to *ADC* about 0.4 cm^2/sec. However, for other choices of pulse sequences, the criterion on *ADC* could be different, while criterion on r and R should remain universal. This demonstrates advantages of using *in vivo* lung morphometry approach as compared to standard *ADC* measurements.





Conclusion: *In vivo* lung morphometry with hyperpolarized ^{3}He allows non-invasive monitoring of emphysema progression at the alveolar level.

References: **1**. Yablonskiy DA, *et al*, PNAS 2002; 99: 3111-3116. **2**. Sukstanskii AL, Yablonskiy DA, J Magn Res 2007, in press. **3**. Haefeli-Bleuer B, Weibel ER, *Anat Rec* 1988; 220: 401-414.

Supported by NIH R01 HL70037 and R01 HL72369 and an equipment loan from General Electric for use of their ^{3}He polarizer.