Time Dependence of ^{3}He Diffusion in the Human Lung: Measurement in the Long-time Regime Using Stimulated Echoes

C. Wang[1], G. W. Miller[2], T. A. Altes[2,3], E. E. de lange[2], J. P. Mugler, III[1,2]

[1]Dept. of Biomedical Engineering, University of Virginia, Charlottesville, VA, United States, [2]Dept. of Radiology, University of Virginia, Charlottesville, VA, United States, [3]Dept. of Radiology, Children's Hospital of Philadephia, Philadelphia, PA, United States

Introduction: Hyperpolarized ^{3}He diffusion MRI of the human lung, which permits non-invasive characterization of the pulmonary microstructure, has been explored in two different time-scale regimes. Short-time-scale measurements (1), which use a diffusion time on the order of a millisecond, probe structure at the alveolar level, whereas long-time-scale measurements (2,3), which use a diffusion time on the order of a second, probe structure at the acinar level and likely yield information on the connectivity among the small airspaces. It has been hypothesized that long-time-scale measurements may be more sensitive to diseases such as emphysema that affect the small- and medium-sized airspaces (3), providing the impetus for development of robust and reproducible long-time-scale measurement techniques. Although one would suspect that the long-time-scale apparent diffusion coefficient (ADC) might show a strong dependence on diffusion times on the order of a second, existing methods yield a value that is an average over several seconds. Thus, these methods can neither detect potential variations in the ADC with changes in the diffusion time, nor measure the ADC at a specific diffusion time. To address these issues, we developed a stimulated-echo-based pulse sequence that can measure the ADC over a range of diffusion times in one breath-hold acquisition, thereby permitting the relationship between the ADC and diffusion time to be characterized in the long-time-scale regime. The purpose of the present study was to validate this pulse sequence using computer simulations, phantom measurements and preliminary in-vivo studies in healthy and diseased human lungs.

Methods: Our method for long-time-scale ADC measurements was implemented in two modes: as a global measurement, in which the average diffusivity over the entire lung is measured at diffusion times ranging from a few tenths of a second to several seconds, and as a two-dimensional imaging procedure, in which the regional distribution of ADC values is measured within one or multiple slices at a single diffusion time of 1.5 s. Both implementations begin with the measurement of (non-diffusion weighted) reference signals to correct for the effects of signal decay due to T1 relaxation and the application of RF pulses, and to estimate the signal level just before a pair of adiabatic 90° RF pulses, between which is applied the first of two (for each measured signal) diffusion-sensitization gradient pulses to generate modulated longitudinal magnetization with a selected "tag" wavelength. Following the 90°-90° pulse pair, a series of stimulated echoes are collected, each following an α° excitation RF pulse and the second diffusion-sensitization gradient pulse (4). For the imaging case, successive stimulated echoes are phase encoded. In contrast to a straightforward adaptation of previous stimulated-echo methods (4), the use of reference signals permits the required data to be collected in one breath-hold acquisition.

Computer simulations were performed to determine the sensitivity of our technique to noise and to variations in experimental (e.g., tag wavelength) or physical (e.g., relaxation times) parameters, and to guide the selection of parameter values for experimental studies, including tag wavelength, flip angle and diffusion time. Phantom studies were performed in a Tedlar plastic bag (50-100ml hyperpolarized ^{3}He and 950-900ml N_2) to test our method under conditions of nearly free diffusion. All experimental studies were done on a 1.5-T scanner (Siemens Sonata). ^{3}He gas was polarized to ~35% by collisional spin exchange with an optically pumped rubidium vapor using a commercial system (Model 9600, MITI).

Ten healthy volunteers (5 male, 5 female; age range 21-74 years) and two subjects with COPD (1 male, 1 female; ages 70 & 73 years) were imaged. Global diffusion measurements (with diffusion sensitization in the anterior-posterior direction) were obtained for all subjects at breath hold following inhalation of 50-80 ml hyperpolarized ^{3}He gas diluted with N_2 to a total volume of 1 liter. The identical procedure was repeated in three of the subjects to evaluate the reproducibility of the technique. In three of the subjects, measurements were also obtained with diffusion sensitization along the other two principal axes (head-foot and left-right). Projection long-time-scale ADC maps were acquired in both COPD patients and in two of the healthy volunteers at a diffusion time of 1.5 s. Short-time-scale ADC maps were also acquired by using a gradient-echo-based diffusion technique (bipolar diffusion sensitization) with b values of 0 and 1.6 s/cm^2.

Results: Computer simulations indicated that our method should be robust against anticipated variations in experimental parameters such as T1, T2, T2* and SNR. Measured ADC values in the Tedlar-bag phantom (~0.8 cm^2/s for global ADC and 0.86±0.12 cm^2/s for projection ADC map) were close to the predicted free diffusion coefficient (0.83-0.88cm^2/s) of ^{3}He in air and decreased slightly with increasing diffusion time, consistent with the situation of nearly free diffusion. In the lung, however, long-time-scale ADC values were more than an order of magnitude less than the free diffusion coefficient and decreased markedly with increasing diffusion time, consistent with severely restricted diffusion. Graphs of global ADC versus diffusion time for the ten healthy subjects are shown in Fig. A. Mean values were 0.039 and 0.023 cm^2/s at diffusion times of 0.61 and 1.54 s, respectively. Reproducibility was good, with RMS differences less than 4% for each of the repeated measurements, and the anisotropy experiments consistently yielded higher ADC values in the head-foot direction. ADC maps were generally uniform (Fig. C) with mean values similar to corresponding global values. For the two COPD subjects, global ADC values were substantially greater than those of every healthy subject at all diffusion times measured (Figs. A, B) and increased approximately 100% compared to mean values for healthy subjects. Regional elevations of ADC values were far more conspicuous on long-time-scale ADC maps (Fig. D) than on short-time-scale ADC maps (Fig. E).

Conclusion: A stimulated-echo-based technique was developed for measuring the long-time-scale ADC of hyperpolarized ^{3}He in the human lung during a single breath-hold, optimized by computer simulations, and used in ten healthy subjects and two subjects with COPD to measure the global ADC for diffusion times ranging from 0.3 to 10 s, and to acquire spatial maps of the ADC for a diffusion time of 1.5 s. In healthy subjects, the global ADC values decreased by several-fold over the range of diffusion times measured. In two COPD subjects, global ADC values were substantially greater than those of the healthy group and focal areas of increased ADC were more conspicuous on long-time-scale ADC maps than on short-time-scale ADC maps. These preliminary results suggest that our technique may provide, compared to short-time-scale ADC techniques, improved sensitivity to the microstructural changes that occur in the lung with emphysema.

References:

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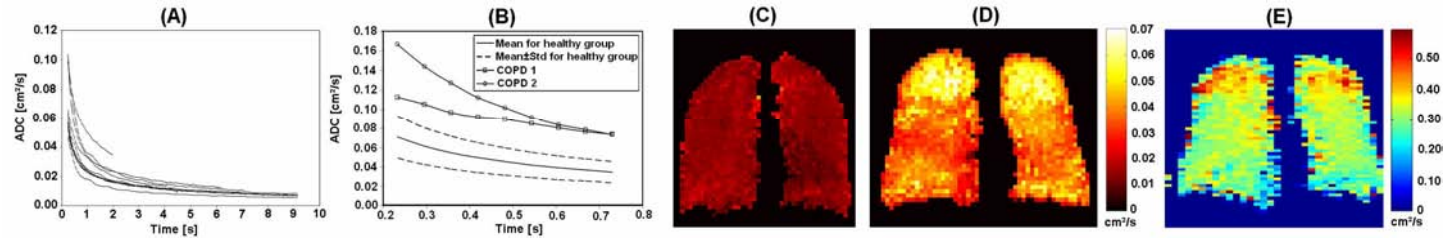

A) Global long-time-scale ADC versus diffusion time for ten healthy subjects. **B)** Global long-time-scale ADC versus diffusion time for the COPD subjects compared to overall results from the healthy group. **C and D)** Coronal projection long-time-scale ADC maps from a healthy subject (C) and from a subject with sub-clinical (GOLD stage 0) COPD (D). In (D), ADC values are markedly in the lung apices and moderately elevated in the mid lung. **E)** Coronal projection short-time-scale ADC map from the same subject with sub-clinical COPD, showing mildly elevated ADC values in the apices.