# Experimental measurements and computer simulation of long-time-scale hyperpolarized $^3$He and $^{129}$Xe diffusion in human lungs

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**Introduction:** Hyperpolarized noble-gas diffusion MRI of the lung can be used to obtain information about the pulmonary microstructure [1,2]. It has been suggested that long-time-scale $^3$He diffusion measurements may be more sensitive than short-time-scale measurements to the early changes in emphysema [2,3]. However, even in healthy subjects, the relationship between long-time-scale diffusion measurements and the complex lung structure is not well understood. Further, to our knowledge, long-time-scale $^{129}$Xe diffusion in human lungs has not been previously measured. The purpose of this study was to investigate the diffusion-time dependence of $^3$He and $^{129}$Xe diffusion measurements in human lungs, and to compare the experimental measurements with theoretical simulations based on a multiple-branch-point model of the human acinus [4].

**Methods:** A series of global apparent diffusion coefficient (ADC) values (i.e., integrated over the entire lung) were measured at diffusion times ranging from about 0.1 to 5.0 seconds using a stimulated-echo-based method with diffusion sensitization in the anterior-posterior direction [2]. The pulse sequence is described in ref. 2. **$^3$He**: $^3$He diffusion MRI was performed in 29 healthy volunteers (Age: 57±9; 12M, 17F) using a 1.5T scanner (Sonata, Siemens). $^3$He was polarized to ~30% by the collisional spin-exchange technique using a commercial system (Model 9600, MITI). The measurements were obtained from all subjects at breath hold following inhalation of 50 ml $^3$He mixed with 950 ml $N_2$. The tag wavelength was 10 mm. **$^{129}$Xe**: $^{129}$Xe diffusion MRI was performed in 2 healthy volunteers (Age: 43, 48; 1M, 1F) using a 1.5T scanner (Avanto, Siemens). $^{129}$Xe was polarized to 10-20% by the collisional spin-exchange technique using a prototype commercial system (Xemed, LLC). The measurements were obtained at breath hold following inhalation of 250 ml $^{129}$Xe mixed with 500 ml of room air and $O_2$. The tag wavelength was 5 mm. **Simulation**: $^3$He diffusion in the human acinus was simulated by numerically solving a one-dimensional gas transport equation along the axes of all alveolated airways of a multiple-branch-point acinar model. By imposing an initial $^3$He concentration of 1 in any given location of the model ($^3$He concentration being zero elsewhere), and repeating the computation of diffusional $^3$He spread for all different locations in the model, an effective diffusion could be obtained for different time intervals. The free diffusion coefficient for $^3$He mixed in the air was assumed to be 0.88 cm$^2$/s. Simulation details are described in ref. 4.

**Results:** A plot of the measured $^3$He global ADC versus diffusion time shows that, for diffusion times in the range of 200 ms to 5 s, the $^3$He ADC strongly depends on the diffusion time, Fig. 1a. The measured $^3$He ADC at a diffusion time of 1 s is ~ 0.02 cm$^2$/s, which is one order of magnitude less than the $^3$He ADC value for the short-time scale (~0.2 cm$^2$/s for a diffusion time of 1 ms). Similarly, for $^{129}$Xe, the long-time-scale ADC is also approximately one order of magnitude less than that at the short-time scale and strongly depends on the diffusion time, Fig. 1b. The long-time-scale $^{129}$Xe ADC is about 1/5 of the corresponding $^3$He ADC, i.e., similar to the ratio of their free diffusion coefficients in air ($^{129}$Xe 0.14 cm$^2$/s, $^3$He 0.88 cm$^2$/s). The plot of the $^3$He ADC versus diffusion time derived from the acinar-model simulation has a very similar appearance to the experimental measurements, Fig. 1c. To facilitate comparison, the above three curves were plotted together after normalizing each by the corresponding free diffusion coefficient in air, Fig. 1d.

**Discussion:** The agreement between $^3$He computer simulations in an acinar model and experimental $^3$He ADC measurements suggests that the long-time-scale ADC as measured by diffusion MRI reflects effective diffusion in the complex acinar structure of the lung. The slight underestimation of ADC by the simulations for diffusion times greater than 3 s indicates that for these time intervals, pathways between groups of acini may need to be considered. In addition, long-time-scale $^{129}$Xe diffusion was measured in human lungs for the first time, and showed a dependence on the diffusion time similar to that for long-time-scale $^3$He diffusion. After normalization by their respective free diffusion coefficients, $^3$He and $^{129}$Xe diffusion measurements, and their dependence on time, were also similar, suggesting that long-time-scale $^3$He and $^{129}$Xe diffusion probe similar structures. Thus, $^{129}$Xe diffusion has the potential to replace $^3$He diffusion for the evaluation of the lung microstructure.

**Conclusion:** Long-time-scale $^3$He and $^{129}$Xe diffusion depend on the diffusion time, and the ADC values for both gases were one order of magnitude less than the corresponding short-time-scale ADC values. Computer simulations based on an acinar model closely matched the experimental measurements, suggesting that noble gas diffusion is in large part representative of the complex intra-acinar pathways in the lung periphery.

**References:**

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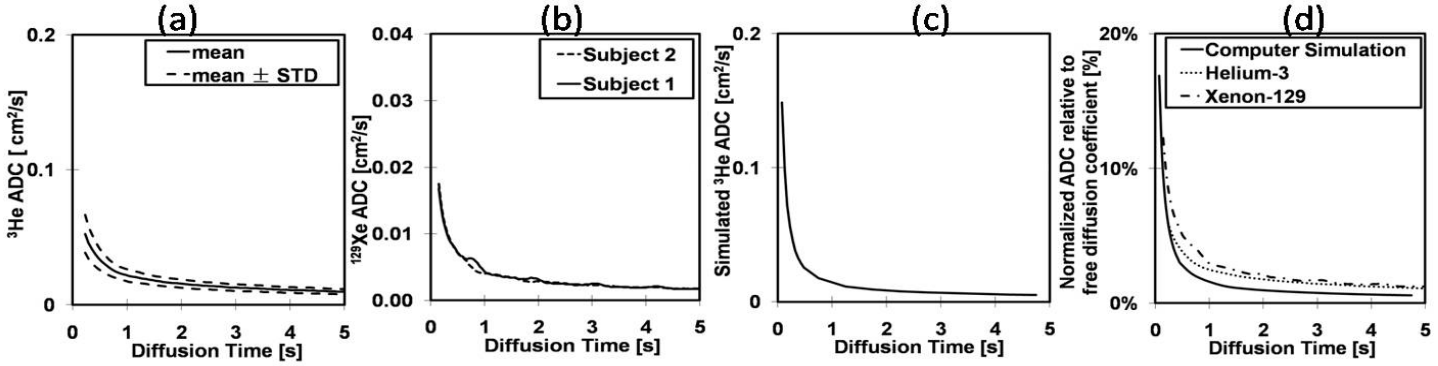


**Figure. 1: (a)** Measured $^3$He ADC versus diffusion time in 29 healthy volunteers. **(b)** Measured $^{129}$Xe ADC versus diffusion time in 2 healthy volunteers. **(c)** Simulated $^3$He ADC versus diffusion time using an acinar model. **(d)** Normalized ADC versus diffusion time for simulated $^3$He, and experimental $^3$He and $^{129}$Xe measurements.