Anisotropic Nature of 3He Gas Diffusion in Mice Lungs

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Introduction: Lung morphometry technique that utilizes 3He MRI [1, 2] demonstrated in vivo quantification of lung geometrical parameters in humans, comparable to those obtained through histology. As part of the broader effort, this technique, optimized for mouse lungs, allowed us to calculate mouse lung geometry comparable to histological findings. In our approach, lung airways are considered as cylinders covered by alveolar sleeve; diffusion of 3He atoms in airways is described by two distinct diffusion coefficients D_L (along airway) and D_T (perpendicular to airway axis). Diffusion-attenuated MR signal in such a microscopically anisotropic but macroscopically isotropic system (the uniform orientation distribution of airways is assumed) is non-mono-exponential in *b*-value in human [1, 2] and mice. However, such a non-mono-exponential dependence can, in principle, be caused by other factors, e.g., due to the presence of multiple spherical compartments (that mimic alveoli) with a variety of sizes. We used a *triple*-gradient pulse sequence consisting of 3 consecutive bipolar gradient pairs with orthogonal gradient orientations (e.g., along the Cartesian axes *X*, *Y*, *Z*) to prove that diffusion of 3He gas in the mice lung acinar airways is really microscopically anisotropic.

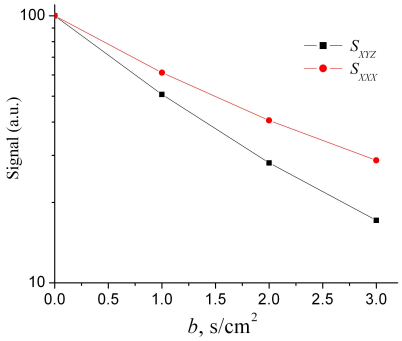
Methods: To distinguish microscopically anisotropic but macroscopically isotropic system from a microscopically isotropic system, a double-vector MR experiment, in which the diffusion sensitizing gradients are applied consequently in two orthogonal directions, was proposed in [3]. We exploit the same idea expanding it to a triple-vector sequence to avoid potential uncertainties of the two-vector experiment that could take place in a system of uniaxial symmetry. Besides, the MR signal in the triple-vector experiment can be described by a simple analytical expression, which is not available for a two-vector experiment. In our approach, we are comparing the signal acquired with three successive gradient pairs (each pair is characterized by the same given *b*-value) applied in three mutually orthogonal directions, S_{XYZ}, and the signal acquired with three successive gradient pairs applied in the same direction, S_{XXX}. For a microscopically isotropic system characterized by a single diffusion coefficient D_{iso}, e.g., spherical pores, both the signals will be the same and proportional to $\exp(-3bD_{iso})$. For a microscopically anisotropic system of cylindrical symmetry, characterized by two diffusivities D_L and D_T, the signal S_{XYZ} is also mono-exponential in *b* value, $S_{XYZ} \sim \exp(-3b \cdot ADC)$, $ADC = (D_L + 2D_T)/3$. Whereas in the *XXX*-experiment, the signal, $S_{XXX} \sim \sqrt{\pi/12b \cdot (D_L - D_T)}\exp(-3b \cdot D_T) \cdot \mathrm{erf}\left(\sqrt{3b \cdot (D_L - D_T)}\right)$, is non-mono-exponential in *b* [1]. Note also that $S_{XYZ} < S_{XXX}$ at any *b*.

Gas Preparation: Commercial General Electric polarizer was used to produce ~1 L of 3He gas at ~40%-50% polarization level. Prior to experiments the gas was transferred to a 1 L Tedlar bag, which was kept in fringe field during a course of several experiments on one mouse lungs.

Lung Preparation: Six mice were used for this study. We used lungs excised from freshly sacrificed mice (C57BL/6N, males, 3-4 months old, 21-27 grams). Mice were euthanized using 0.1 ml of Ketamine and lungs were extracted. Then trachea was tied around a plastic needle to ensure tight seal. Using a setup consisting of six valves, lungs are repeatedly purged with ^{3}He to dilute oxygen and other gases out of the lungs. HP ^{3}He is brought to the fringe field of the magnet. Using the same 6-valve setup, any oxygen that got into the system through connecting the Tedlar bag to the 6-valve setup, is purged. At this point ~850 µl HP ^{3}He gas is delivered to the lungs, and topped with ~150 µl of N_2 to eliminate ^{3}He MR signal contribution from the non-acinar portion of the lung. Tedlar bag is disconnected and the lungs are ready to be scanned. Besides keeping the oxygen out, the main objectives of the 6-valve system are repeatable delivery of HP ^{3}He at the consistent lung inflation and a precise topping with N_2 blanket.

MR Experiment: The data were collected on a Varian 4.7T scanner with 120 mm horizontal bore equipped with 60 G/cm gradients. Diffusion time used in human experiment [1] was 1.8 ms, which was small enough for the ^{3}He molecule to remain inside of single acinar airway. In mice, airways are smaller and we used much shorter diffusion times. Thus, we used bipolar diffusion-sensitizing gradients ($\Delta = \delta = 0.35$ ms), with fixed ramp times ($\tau = 0.175$ ms) and 4 *b*-values ranging from 0-3 s/cm^2

Results: Figure demonstrates typical MR signals dependence on *b*-value for the *XYZ*- and *XXX*-experiments (log scale), obtained from one mouse (signals from all others mice demonstrate similar behavior). As expected, the signal corresponding to the *XYZ* experiment is practically mono-exponential and lays below the signal corresponding to the *XXX* experiment. This difference between the signals proves that non-mono-exponential behavior of the MR signal is indeed due to the diffusion anisotropy at the microscopic level.



Conclusion: In this abstract we provided evidence that the non-monoexponential behavior of diffusion attenuated MR signal of ^{3}He gas in lungs is caused by macroscopically isotropic but microscopically anisotropic nature of ^{3}He gas diffusion in lung acinar airways.

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