Relationship between 3He gas ADCs and lung microstructure. Computer Simulations

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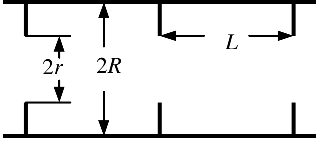
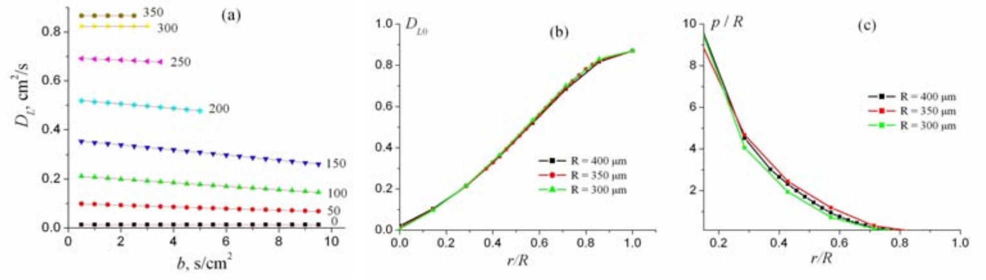
Introduction: The *in vivo* lung morphometry technique [1] allows evaluation of lung microstructure based on MRI measurement of diffusion of hyperpolarized ^{3}He gas. In this approach, acinar lung airways are considered as cylinders covered by alveolar sleeves [2]. Diffusion of ^{3}He gas in each airway is anisotropic and described by distinct longitudinal and transverse diffusion coefficients, D_L and D_T. An analytical expression for the diffusion MR signal as a function of *b*-value was derived taking into account the fact that a multitude of uniformly oriented airways are present in each imaging voxel. This macroscopically isotropic but microscopically anisotropic model allows estimation of D_L and D_T from multi *b*-value MR experiments [1]. Also, an analytical expression was derived relating the transverse diffusion coefficient D_T to the airway radius R that made it possible to estimate R despite the airways being too small to be resolved by direct imaging. The results obtained in [1] are in good agreement with histological data for healthy human lungs [2]. Computer simulations of ^{3}He gas diffusion in alveolar ducts [3] also demonstrate good agreement with results of this model. However, a relationship between the longitudinal diffusion coefficient D_L and the structure of alveolar sleeves was not established previously. This is the subject of the present study.

Methods: According to the model [2] adopted in [1], an acinar airway is considered as a cylinder of radius R covered by a sleeve of alveoli. To study the role of the alveolar sleeve on longitudinal gas diffusion, we mimic an airway by a structure shown in Fig. 1. ^{3}He atoms can freely diffuse within the internal cylinder of radius r; however, the alveolar walls (internal and external) are impermeable to the gas atoms.



Computer simulations of random-walks were performed on N=10^7 independent particles with random starting positions. At each step of duration $\Delta t = 1\mu s$, a particle moves with equal probability in one of 8 directions (±1, ±1, ±1) over distance $l_0 = (6D_0 \cdot \Delta t)^{1/2}$, where D_0=0.88 cm^2/s is the free diffusion coefficient of ^{3}He gas diluted in air. At each position, a particle gains a phase $\Delta\varphi = \gamma \mathbf{G}(t)\mathbf{r} \cdot \Delta t$, where γ is the gyromagnetic ratio, and $\mathbf{G}(t)$ is a time-dependent magnetic field gradient introduced in a standard manner for diffusion encoding. In the simulations, we chose $\mathbf{G}(t)$ corresponding to the gradient echo pulse sequence with diffusion time Δ = 1.8 ms and up- and down ramp time 0.3 ms (similar to [1]).

Results: Fig.2 illustrates results of simulations for the longitudinal diffusion obtained with diffusion gradient parallel to the cylinder's axis. The dependence of D_L on the *b*-value (shown by symbols in Fig. 2a) for different internal radii r (shown by numbers near the lines, in μm) is presented for $R = L = 350\,\mu\text{m}$ that corresponds to a typical alveolar duct size in healthy lungs (data shown are restricted to fixed gradient pulse sequence timing and $bD_L < 2$). In the case $r = R$ corresponding to free diffusion, $D_L = D_0$ and does not depend on *b* value. For all other values of $r < R$, the dependence D_L on b can be well approximated as linear function $D_L = D_{L0}(1 - p \cdot bD_{L0})$ (shown by color lines). Simulations with different external radii (R = L = 300, 350, and 400 μm) reveal practically identical dependences of D_{L0} and p/R on the ratio r/R for different R (Fig. 2b and Fig. 2c). These remarkable scaling relationships are not obvious because there is one more dimensionless parameter in our simulations $- R/L_0$, where $L_0 = (6D_0 \cdot \Delta)^{1/2}$ is the diffusion distance. In the physiological interval $0.3 < r/R < 0.7$, D_{L0} can be approximated by a straight line: $D_{L0} = D_0 \cdot (1.32 \cdot r/R - 0.15)$. The parameter p depends on r/R exponentially: $p/R = 21.38 \cdot \exp(-5.39 \cdot r/R)$. For selected parameters of diffusion gradient waveform and typical parameters of lung airways, the dependence of transverse diffusion coefficient D_T on the gradient strength is substantially smaller than in the case of D_L.



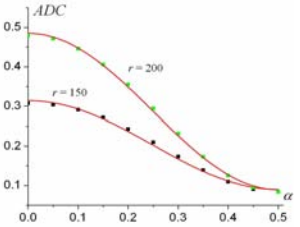


Fig. 3 illustrates the dependence of ADC (calculated as $ADC = -b^{-1} \ln S(b)$) on the angle α between airway axis and diffusion gradient ($b = 5\,\text{s/cm}^2$, $R = L = 350\,\mu\text{m}$) for $r = 150\,\mu\text{m}$ (black dots) and $r = 200\,\mu\text{m}$ (green dots). An excellent fit of the function $D_L \cos^2\alpha + D_T \sin^2\alpha$ to the simulated data (red lines) means that for given geometrical parameters (and pulse sequence timing) the longitudinal and transverse diffusion can be separated despite of the presence of the alveolar sleeves.

Conclusion: Our simulations reveal that, due to the presence of the alveolar sleeves, the longitudinal diffusion coefficient linearly depends on *b*-value. As a result, the signal dependence on *b*-value even in a single cylinder (airway) becomes non-monoexponential. This dependence can be readily incorporated into the model function [1] used for post-imaging analysis of experimental data, *p* being an additional fitting parameter. In the physiologically important range of the ratios r/R, D_{L0} depends on r/R linearly; the parameter p depends on r/R exponentially.

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