A theory of diffusion time dependence of ADC in hyperpolarized 3He lung MRI. Millisecond range

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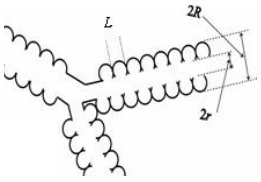
Introduction: Lung diffusion MRI with hyperpolarized ^{3}He gas provides information on lung structure and function. Substantial increases in ADC have been reported in emphysema suggesting that ^{3}He gas ADC could serve as a biomarker for disease progression. However, even in healthy human lungs ADC exhibits rather broad variability, with different studies reporting results between 0.15 cm^2/s and 0.25 cm^2/s. Here we provide a theoretical analysis demonstrating a significant diffusion time dependence of ADC, even for diffusion times on the order of several milliseconds, which can explain the observed ADC variability.

Theory: The *in vivo* lung morphometry technique (1) allows evaluation of lung microstructure based on MRI measurements of the diffusion of hyperpolarized ^{3}He gas. According to the lung geometric model (2) adopted in (1), an acinar airway is considered as a cylinder covered by a sleeve of alveoli (see Fig. 1). In humans, depending on the branching level of the acinar airway tree, the internal acinar airway radius r varies in the interval from 135 μm to 250 μm, whereas the outer radius R (including the sleeve of alveoli) remains practically constant at 350 μm (2). ^{3}He atoms can freely diffuse within the internal cylinder of radius r; however, the alveolar walls (internal and external) are treated as impermeable to the gas atoms. Hence, 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 that a multitude of airways are present in each imaging voxel, with a uniform distribution of orientations. This model allows estimation of D_L and D_T from multi b-value MR experiments (1). In most experimental studies of gas diffusion in the lungs, only the mean isotropic ADC is determined from measurements with small b-values. In this limit, ADC has a simple relationship to D_L and D_T (1):



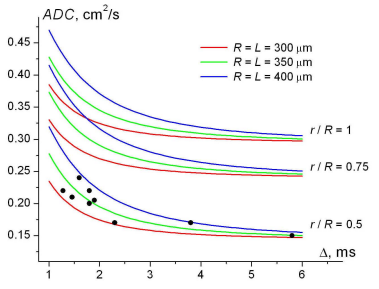
$$ADC = \left(D_L + 2D_T\right)/3 \qquad [1]$$

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 (3):

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

Here D_0 is the quasi-free diffusion coefficient of ^{3}He gas in lung airspaces; $L_{diff} = \left(4D_0\Delta\right)^{1/2}$ is the characteristic free-diffusion length for two-dimensional diffusion. Equations [2] are valid for $R/L_{diff} < 0.5$ and $r/R > 0.4$. Eqs. [2] predict that the longitudinal diffusivity D_L does not depend on the diffusion time Δ, whereas the transverse diffusivity D_T decreases as Δ increases. In the limiting case $R \ll L_{diff}$, $D_T \to 0$ and ADC is completely determined by the longitudinal diffusivity D_L: $ADC \approx D_L/3$ and is independent of Δ. This result is valid only when $(2D_L\Delta)^{1/2}$ is smaller than the mean length of alveolar ducts (~ 1 mm); hence, assuming a typical $D_L \sim 0.4$ cm^2/s, the diffusion time should be less than 12 ms. For longer diffusion times, a theory accounting for branching of acinar airways is required (4). Although D_T is smaller than D_L, for R ~ 300-400 μm (radii characteristic to human lungs) and Δ about several milliseconds, its contribution to variations in ADC is substantial.

Results and Discussion: Figure 2 illustrates the dependence of ADC on Δ for different external radii R and ratios r/R (colored lines) obtained from Eqs. [1,2] with $D_0 = 0.88$ cm^2/s. Note the significant dependence of ADC on r/R, whereas its dependence on R is comparably weak. Black dots in Fig. 2 correspond to ADCs experimentally found in healthy human lungs, found for different Δ in (5). Also we included single-Δ results from (1, 6-10). All of these ADCs fall within an interval of R around 350 μm (in good agreement with histological data (2)) and correspond to $r/R \approx 0.5$. The dependence on diffusion time Δ of this data is nicely explained by Eqs.[1]-[2]. The experimental results presented in Fig. 2 correspond to healthy human lungs. In lungs with emphysema, the ADC is higher. The increase of ADC at initial stages of emphysema (ADCs ~ 0.3-0.4 cm^2/s for Δ ~ 1-2 ms) could be attributed to increasing the ratio r/R (internal alveolar walls are being destroyed). In lungs with severe emphysema, ADCs ~ 0.6-0.7 cm^2/s were observed, e.g., (1, 4), which is significantly higher than predicted by Eqs. [2], even for $r/R = 1$. At this stage of disease, the external walls of airways are being destroyed and the "cylindrical" model of airways becomes invalid.



In small rodents, the radius R ~ 100-200 μm, transverse diffusion is very restricted and D_T is very small. In this situation, $ADC \approx D_L/3$. This result is in a good agreement with experimental data obtained in rat lungs (11): $D_L = 0.3$ cm^2/s, $D_T = 0.01$ cm^2/s, $ADC = 0.11$ cm^2/s. This value of D_L corresponds to $r/R = 0.37$. To observe time dependence of ADC in the lungs of small animals, diffusion times less than 0.5 ms are needed.

Conclusion: Experimentally detected variability of ^{3}He ADC in healthy human lungs can be explained by the substantial dependence of ADC on diffusion time, even over the narrow millisecond range.

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