The influence of diffusion time on the measurement of the short-range ^{3}He diffusivity in human lungs

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Introduction: Measurements of the apparent diffusion coefficient (ADC) of hyperpolarized ^{3}He gas are sensitive to lung microstructure [1]. The 'cylinder model' [2, 3] has been proposed for the estimation of the dimensions of airways from ^{3}He diffusion data using equations obtained from computer simulations in simplified models of acinar airways. However, the behaviour of the diffusion signal is determined not only by the restrictions imposed by the lung geometry, but also depends on diffusion time and strength of the diffusion gradient [4,5]. It has been shown experimentally [5] that the cylinder model does not describe accurately the behaviour of the diffusion signal in the presence of: i., strong diffusion gradients [5], ii.,B_0 dependent susceptibility gradients [6], and iii., time dependent ^{3}He diffusion behaviour [7]. This is significant since the time dependence of ^{3}He diffusion, as predicted by the cylinder model, has been used over a broad range of diffusion times (1.6 - 10 ms) [3, 8], to extract information about the nature of the morphological changes caused by emphysema in human lungs. In this work, the effect of diffusion time on ^{3}He ADC is investigated through experiments with healthy human volunteers. The results of the experiments confirm the predictions of the computer simulations [7], and demonstrate limitations of the cylinder model for reliable lung morphometry measurements.

Methods: In vivo experiments were conducted on 3 healthy volunteers with local ethics approval. All volunteers were scanned using a 1.5T (GE HDx) whole body MRI system with an inhaled gas mixture consisting of 300 ml hyperpolarized^{3}He and 700 ml N_2. For all scans, the subject exhaled to functional residual capacity (FRC) and then inhaled the hyperpolarized gas mixture from a 1L Tedlar bag. Repeated diffusion scans showed that the level of lung inflation (FRC+1L) was reproducible for each subject with ADC variations < 2% between inhalations. The position of the slices was planned using localizer scans acquired with the ^{1}H body coil after inhalation of 1L of air to recreate the ^{3}He breath-hold position. A 2D spoiled gradient echo (5 slices 64x64 matrix, TR: 8.0 ms, FOV:35 cm) with bipolar diffusion gradients (rise and fall times 0.3 ms, no delay between pulses) was used and the slices were acquired consecutively, with slice thickness 15mm and 10 mm spacing. Four sets of diffusion scans were performed for each volunteer with diffusion times: 1.4, 1.6, 1.8 and 2.5 ms. Each scan consisted of 6 interleaved b values (maximum b ~7.5 s/cm^2); the first and last interleave had b = 0 s/cm^2 in order obtain flip angle maps for correction of RF depletion effects.

Results and Discussion: Figure 1 shows the normalized diffusion signal (S/So) decay (averaged over the whole lung) and the average diffusivity (ADC= -ln(S/So)/b) obtained from one of the subjects. The ADC decreases for all of the b values with increasing diffusion time, as shown previously [4] and as expected by the increased motional averaging. The data of Figure 1 was fitted to a stretched exponential [9] to assess the degree of non-Gaussian behaviour. The results demonstrated that while the diffusivity (DDC) decreased considerably with increasing diffusion time (from 0.142 cm^2/s at 1.4ms to 0.090cm^2/s at 2.5 ms), the heterogeneity index α changed by less than 2.5% (0.860 to 0.844). This could indicate that the degree of non-Gaussian behaviour of the signal remains constant and that α may provide a diffusion time independent measure (within the range of diffusion times explored here) of the complexity of the geometry of restricting boundaries. In future work, we plan to explore the behaviour of α at different diffusion time scales (e.g. long range diffusion).

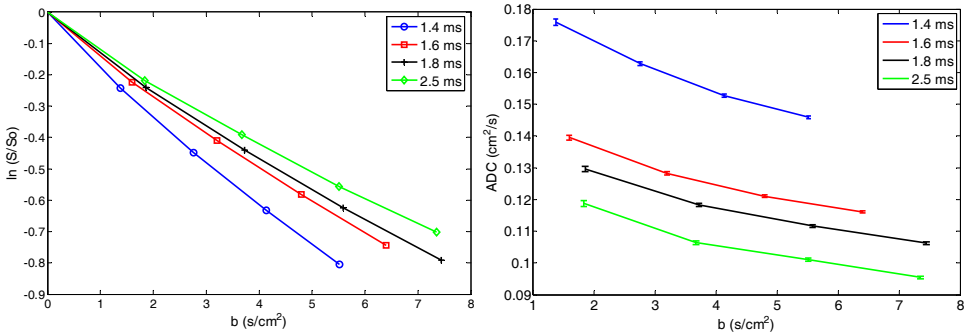

Figure 1. Average lung ^{3}He diffusion signal (left) and ADC (right) values as a function of b obtained from a healthy volunteer.

The diffusion data was also fitted to the cylinder model [2,3] to estimate the average airway dimensions (outer radius R and inner radius r) as well as the mean linear intercept Lm. If the cylinder model correctly describes the diffusion time dependence of ^{3}He diffusion in the lungs, the estimated dimensions should remain constant between acquisitions for each subject at the same lung inflation level. Figure 2 shows the results of those estimates. These experimental results confirm previously presented computer simulations [6] that the cylinder model does not account correctly for the diffusion time dependence. Both R and r decrease with increasing diffusion time, most significantly r (r increases 37% from 1.4 to 2.5 ms, while R increases 11%). These changes in the estimated airway dimensions result in a ~30% change in the Lm value. The lack of diffusion time dependence of the parameter D_{L0} [2,3] of the cylinder model, which was identified in [6], may be one of the major error sources in the estimates.
These errors would be even more significant at larger diffusion times (e.g. 10 ms as used in [8]) and may be even more important for emphysematous lungs where ^{3}He diffuses more freely. Note that in [8] the lack of diffusion time dependence of D_{L0} was exploited to infer the type of structural changes produced by emphysema.

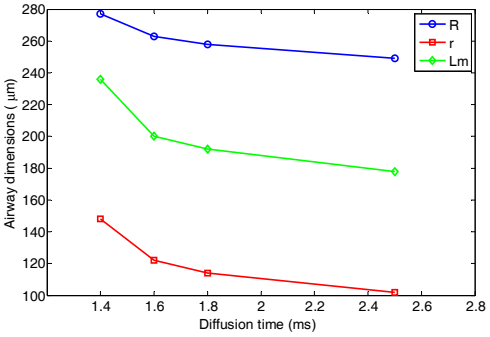

Figure 2. Average lung airway dimensions (R and r) and mean linear intercept Lm estimated from diffusion data from one subject obtained at different diffusion times.

Conclusion: The results of this work show that the short-range ADC of ^{3}He gas in human lungs decreases with increasing diffusion time, while its degree of non-monoexponentiality remained constant in the range 1.4-2.5 ms. The results demonstrate that the cylinder model produces inaccurate estimates of the airway dimensions as a consequence of incompletely accounting for the diffusion-time dependence in the model equations. Further development and validation of this model is necessary before it can be used to accurately assess lung microstructure as the error levels found in r, R and Lm are significant.

Acknowledgements: Funding from EU Phelinet and Airprom networks and EPSRC (EP/D070252/1)

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