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The influence of lung airways branching structure and diffusion time on measurements and models of short-range ^{3}He gas MR diffusion

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ABSTRACT

Hyperpolarized ^{3}He diffusion experiments have been shown to be sensitive to changes in acinar structure due to emphysematous lung disease. Extracting quantitative information about lung microstructure from the diffusion signal is complicated due its dependence on a number of factors including diffusion time and the complex branching acinar geometry. A theoretical model (cylinder model) has been proposed as a means of estimating acinar airway dimensions from measured diffusivities. This model assumes that the effects of acinar branching geometry and finite airway length upon ^{3}He diffusion behaviour are negligible. In this work, we use finite element simulations of diffusion in a model of branching alveolar ducts to investigate in detail the effects of acinar branching structure and finite airway length on short-range ^{3}He diffusion measurements. The results show that branching effects have a significant influence upon ^{3}He diffusivity, even at short diffusion times. The expressions of the cylinder model theory do not account for significant dependences upon diffusion time, branching geometry and airway length, as a consequence of the oversimplified geometrical model used. The effect of diffusion time on ^{3}He ADC was also investigated through experiments with healthy human volunteers. The results demonstrate that the cylinder model can produce inaccurate estimates of the airway dimensions as a consequence of incompletely accounting for the diffusion-time dependence in the model equations and confirmed the predicted limitations of the cylinder model for reliable lung morphometry measurements. The results and models presented in this work may help in the development of a more realistic theoretical framework for 'in vivo lung morphometry' using ^{3}He diffusion MR.

1. Introduction

Hyperpolarized gas (^{3}He and ^{129}Xe) MRI provides information related to the microstructure and physiology of the lungs. In particular, ^{3}He diffusion experiments have been shown to be sensitive to changes in acinar structure due to emphysematous lung disease [1–4]. Most of the in vivo experiments reported to date have measured the apparent diffusion coefficient (ADC) of ^{3}He with pulsed gradient (PG) methods at diffusion times of a few milliseconds.

The diffusion of ^{3}He gas in lung airways exhibits a non-Gaussian phase dispersion [5], which results in a non-mono-exponential signal decay, which cannot be accurately described by a single-ADC model. This signal behaviour originates from effects related to the complex lung geometry such as: airway anisotropy, varying airway dimensions and branching structure [6].

Yablonskiy et al. [7] pioneered a technique that uses a theoretical model to obtain estimates of the alveolar duct diameter from diffusion weighted ^{3}He MR images of human lung. The duct diameter estimates in patients with emphysema were significantly larger than in normal lungs. These results demonstrated the potential of the technique as an in vivo quantitative tool to investigate lung microstructure. In this theoretical analytical model ("cylinder model"), alveolar ducts were considered as infinitely long non-connected cylinders with random orientations. This is on the premise that for short diffusion times, the effects of branching and finite length of airways are negligible. The model also assumes that the non-mono-exponential diffusion signal decay observed in ^{3}He lung MR results from the superposition of the mono-exponential signals originating from Gaussian diffusion in each of the individual airways.

In addition to anisotropic diffusion, other effects can influence the observed signal decay in ^{3}He lung diffusion MR experiments. When large diffusion gradients are used, localized edge enhancement effects [8] cannot be ignored. Susceptibility-induced field inhomogeneities [9] have also been shown to influence the lung ^{3}He diffusion signal behaviour. These effects significantly complicate the determination of accurate relationships between the measured non-Gaussian diffusivities and the lung airway dimensions. This is compounded by the fact that a wide range of experimental

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parameters such as diffusion time Δ, also influence the measured diffusivity.

The cylinder model was further developed by Sukstanskii et al. [10], using a more complex geometrical model, first proposed by Paiva [11], as a basis for Monte Carlo simulations of diffusion. From the simulation results, new expressions for the relationships between ^{3}He apparent diffusivities and the modelled geometric parameters were obtained. These new expressions [10] partially account for non-Gaussian effects by incorporating a first order correction (in b value) to the expressions for the longitudinal and transverse diffusivities. This updated model also assumes infinite non-connected airways. It should be noted though, that all computer simulations in [10] were performed for one diffusion time (Δ = 1.8 ms) only, although it was stated that the resulting theoretical model is valid over a broad range of diffusion times (up to ~10 ms).

In a recent paper [8], we investigated the limits of validity of the cylinder model through a number of purpose-designed experiments in cylindrical phantoms especially designed to fit the geometrical assumptions of the model. This work demonstrated the breakdown of the cylinder model equations for large diffusion gradients (>~15 mT/m) due to the nature of diffusion in the localization regime and we suggested that effects from acinar branching and background susceptibility gradients would further limit the accuracy of the model.

More recently, Sukstanskii et al. [12] published an accuracy analysis of the cylinder model technique. In this study, through computer simulations that incorporate branching geometry, results were obtained that led to the conclusion that branching effects are negligible. Unfortunately this paper only reported the errors that branching effects introduce in the estimated geometrical parameters from the computer simulations; what was not provided were any intermediate results, such as the effect that branching has on the diffusivity parameters of the theoretical model (i.e. D_{L0}, D_{T0}, β_L, β_T, see Appendix A for definitions). It was also stated that the experimental and theoretical evidence of the breakdown of the cylinder model provided in [8] does not apply, this statement was made without identification of any flaws in experimental design in that work.

In [12], background susceptibility effects were incorporated into the computer simulations through the use of analytical expressions describing the localized magnetic field of the distribution of cylindrical alveolar ducts. It was concluded that these effects are negligible at currently used field strengths $B_0 \leqslant 4.7$ T and become only significant (errors in geometrical parameters 16%) at $B_0 = 7$ T. We have recently demonstrated through precise in vivo experiments at two clinical field strengths (1.5 T and 3 T) [8], the significant differences (up to 17%) in measured ^{3}He ADC and estimated airway dimensions that arise as a consequence of background susceptibility gradients at much lower field strength. The discrepancy between those experimental results and the numerical predictions of [12] is due to the oversimplified magnetostatic expressions used in [12] and highlights the importance of solid experimental validation of the foundation assumptions of theoretical expressions derived from numerical modelling.

In the present work, we go on to demonstrate several limitations of the Sukstanskii cylinder model of lung morphometry [12] with respect to the effects that the lung branching structure has on the measured ^{3}He diffusion at different diffusion times.

Evidence of the significant effects that airway branching and finite airway length have upon the measured diffusivities in short-range diffusion experiments already exists in a number of published articles [13–15] that were not cited in [12]. Fichele et al. [13] simulated diffusion in several 2D geometric models using finite difference solution of the Bloch–Torrey equation. The results there indicated that a porous media model was not a good model of lung diffusion. More complex models (i.e. grape and tree-like structures), which included branching and airway connectivity provided results that better matched in vivo diffusion experiments. These results suggested that interconnectivity between airways does play a significant role in acinar diffusion, even for short-time range diffusion.

Plotkowiak et al. [15] also used Monte Carlo simulations to investigate ^{3}He diffusion in a model of a single alveolar sac of finite length. They found that for Δ = 1.9 ms and a single alveolar sac 836 μm long, the simulated average (bulk) ADC values were much smaller than those reported in the literature for healthy lungs. They found that the length of the alveolar sac model had to be increased by about one order of magnitude to unrealistic values of 5.3–12 mm in order to obtain reasonable ADC values, although no quantitative investigation of the diffusivity dependence on airway length was presented.

Computer simulations have also been used by other groups to investigate ^{3}He diffusion in more complex branching structures. Grebenkov et al. [14,16] used Monte Carlo simulations and experiments in a scaled model of a Kitaoka labyrinth [17]. Their results showed that the branching structure does affect the measured diffusivities but concluded that short-range diffusion experiments cannot distinguish the topological structure of the acinus. However, the diffusion time used in this work (Δ = 10 ms) is significantly longer that those typically used for in vivo ^{3}He diffusion studies. The Kitaoka labyrinth also may not be the most realistic model to investigate branching effects for short diffusion times since its geometry is significantly different from the branching structure of acinar airways.

A more realistic geometrical model of the acinar branching structure was used by Perez-Sanchez et al. [18] in Monte Carlo simulations of ^{3}He diffusion at different inflation stages of the breathing cycle. However, no quantitative investigation of the effects of branching and finite airway length upon diffusivity or comparison with other theoretical models was reported.

In this paper, the effects of the lung branching structure and finite airway length in ^{3}He diffusivity in acinar airways are investigated quantitatively for a range of short diffusion times, using finite element computer simulations. The results of these simulations are compared to the theoretical predictions of the latest cylinder model [10,19] and to our previous finite difference simulations [13,20], which did not include branching effects. The diffusion time dependence of the ^{3}He apparent diffusivity was also further investigated experimentally, with quantitative results that significantly deviate from the predictions of the cylinder model. Finally, implications of these results for "in vivo MR lung morphometry" [10] are discussed.

2. Methods

In a typical pulse gradient (PG) diffusion MR experiment, a bipolar gradient (Fig. 1) is applied with varying strength and/or

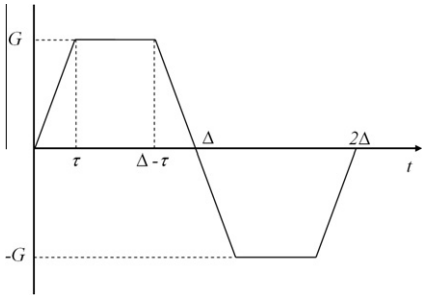

Fig. 1. Diagram of the waveform of the diffusion sensitization gradient used in this work (τ = 0.5 ms, Δ = 1.8–6 ms).