# ON THE VALIDITY OF $^3$HE DIFFUSION MRI EVIDENCE OF NEO-ALVEOLARIZATION IN LUNGS: THE EFFECTS OF BRANCHING STRUCTURE

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**Target audience:** Lung imaging, Diffusion MRI
**Purpose:** To test the validity of using current models of lung morphometry from $^3$He MR diffusion to provide evidence of neo-alveolarization in human lungs

**Introduction**

$^3$He MR diffusion experiments are sensitive to changes in lung microstructure [1]. Recently two papers have reported the use of $^3$He diffusion MR to estimate changes in airway in vivo geometry due to lung growth from childhood to adolescence [2] and in an adult after pneumonectomy [3]. Both studies concluded that the predominant mechanism of lung growth was the increase in the alveolar number rather than the enlargement of existing alveoli. These conclusions are significant for the understanding of lung development and could impact upon therapies. The methods used in these works are based on simplified models of airways that do not account for the branching structure. In addition, the cylinder model [4] has been demonstrated [5] to produce inaccurate estimates of airway dimensions due to incomplete treatment of diffusion time dependence. The rationale behind both papers [2,3] (Fig. 1) is that if lung growth is accomplished by enlargement of existing airways and alveoli, the measured apparent diffusion coefficients (ADC) should increase due to the reduction of restriction to helium diffusion. If the ADC increases less than expected by simple expansion, then the increase in lung volume must be due to growth of new alveoli. In this work we use computer simulations to assess the effect that airways branching has on measurements of ADC in the growing lung and on the interpretation of the data obtained in [2,3].

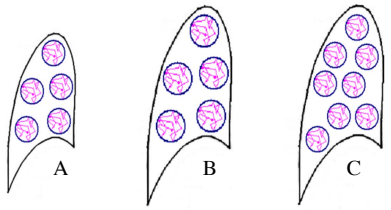


Figure 1. Schematic of the rationale behind the $^3$He diffusion MR methods reported in [2,3]. The initial lung volume (A) can increase by airway enlargement (B), or by growth of new alveoli (C).

**Methods**

Finite element computer simulations of $^3$He diffusion in geometric models of acinar airways were implemented in Comsol Multiphysics. The Bloch Torrey equation was solved for a bipolar diffusion gradient as used in [5] with diffusion times Δ between 1.6 and 6 ms and gradient strength scaled to obtain *b* values between 0 and 8.5 s/cm$^2$.

In these models, an alveolar duct (Fig. 2) consists of alveolated cylindrical segments of length *L*=240 μm, external radius *R*=350 μm and alveolar depth *h*=200 μm.

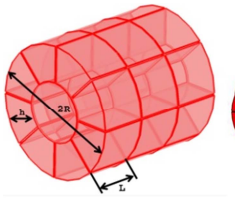


Figure 2. Model of alveolar duct used in the simulations.

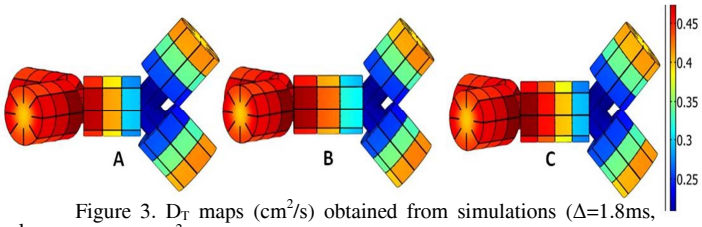


Figure 3. $D_T$ maps (cm$^2$/s) obtained from simulations (Δ=1.8ms, b=8.5 s/cm$^2$) with the original branching model (A) the airway enlargement model (B) and the alveolarization model (C).

To simulate infinite ducts (as in the cylinder model), periodic boundary conditions were used [6]. The original branching model (Fig. 3a) has branches at both ends of a duct with three segments. The diffusion signal was calculated by integration of the transverse magnetization over the central duct only.

To simulate alveolarization a fourth segment was added to the central alveolar duct (i.e. increasing number of alveoli by 33%) while the dimensions (R, h, L) were kept constant (Fig. 3c). To simulate airway enlargement (Fig. 3b), L was increased to 320 μm (33% increase), such that the total duct length was similar to in the alveolarization model. R was not changed, to simulate the findings of [3], that R did not change with increasing lung volume. In the cylinder model framework, the diffusion behaviour is described in terms of two orthogonal diffusivities. Here, the transverse ($D_T$) and longitudinal ($D_L$) diffusion coefficients were obtained from simulations with the diffusion gradient perpendicular and parallel to the central duct, respectively. ADC was calculated from the bulk signal [4]:

$$S(b)= So \exp[-bD_T] [\pi/(4b(D_L-D_T))]^{1/2} \Phi[(b(D_L-D_T))^{1/2}] \quad (1);$$

where Φ(x) is the error function.

**Results and discussion**

Diffusivities in the branching models were larger than in isolated airways by more than 10% for all the diffusion times and b values investigated. As expected, for infinite non-connected airways, the addition of new alveoli causes no change in measured diffusivities, while enlargement of alveoli (increasing L by 33%) increases $D_L$ by 5.4 % but does not change $D_T$, resulting in a small increase in ADC (2.2%).

In the branching model, both $D_L$ and $D_T$ change (~5%, Table 1) with alveolarization (Fig. 3c), while neither change (≤1.1%) with alveolar enlargement (Fig. 3b). This diffusion behaviour, completely different from that observed in non-connected infinite airways, is unique to branching geometries (like acinar airways). Figure 4 demonstrates how the increase of alveolar size L, while keeping R constant (33% volume increase), produces a slight decrease in measured ADC. This result would be interpreted within the framework of the cylinder model as an increase in the number of alveoli (with smaller size than the original alveoli), which is clearly not the case. Furthermore, the cylinder model enforces isotropic airway enlargement by assuming L=0.75R, which has not been demonstrated to hold true through lung growth and inflation, and makes it ill-suited to assess changes in airway dimensions due to growth or volume changes in the breathing cycle [7].

As expected from previous work [5], the cylinder model is not valid for Δ=5.2 ms used in the work of [2] and both *R* and *h* were grossly overestimated (average values: *R*= 426 μm and *h*= 244 μm). Surprisingly the authors of that paper did not realize that those dimensions are larger than average airway dimensions in adults and unreal in a population of children with median age 12.8 years.

Our results indicate that currently used gas diffusion MR techniques and models are inadequate to quantify lung structure changes due to growth and inflation. New more accurate diffusion-based techniques for lung structure quantification may use combinations of different diffusion times and/or gas mixtures.

| | Original model L=240 μm | Airway enlargement L=320 μm | Alveolarization L=240 μm |
|---|---|---|---|
| $D_T$, cm$^2$/s | 0.114 | 0.115 (1.1%) | 0.119 (4.9%) |
| $D_L$, cm$^2$/s | 0.246 | 0.248 (0.8%) | 0.233 (-5.5%) |
| ADC, cm$^2$/s | 0.152 | 0.153 (0.9%) | 0.153 (0.6%) |

Table 1. ADC, $D_L$ and $D_T$ values obtained from computer simulations (Δ=1.8ms, b=8.5 s/cm$^2$). The values in brackets are the diffusivity change with respect to the original model.

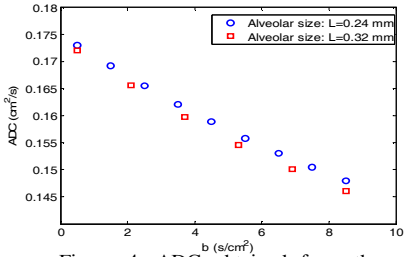


Figure 4. ADC obtained from the original branching model (Fig. 2a) and the airway enlargement model (Fig. 2b).

**Conclusion**

Alveolarization may well have occurred in the subjects investigated in [2, 3], but these papers do not prove it conclusively, since in branching geometries changes in ADC measured with conventional diffusion MR may be the result of different types of structural changes and hence cannot discriminate between airway enlargement and alveolarization.

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**References**

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