Imaging lung microstructure in mice with hyperpolarized ^{3}He diffusion MRI

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Introduction

The ^{3}He diffusion MRI technique for measuring lung morphometry[1,2] has been successfully implemented in human lungs[3] and was developed for the mouse lung *ex vivo*[4]. Non-invasive quantitative measurement of lung microstructure is of great significance in assessment of pulmonary disease, particularly in the earliest stages, and the ability to longitudinally image microstructural changes in mouse models of disease offers particular advantages to studies of pathogenesis, lung regeneration, and treatments[5]. Here we implemented ^{3}He lung morphometry to quantify lung microstructure in the mouse *in vivo*, and validated it against direct quantitative histology.

Methods

Seven normal 12-week-old C57 mice were used, with Animal Studies Committee approval. The mice were ventilated by a custom-built ventilator[6] at 120 breaths per minute with 0.25-mL tidal volume, and anesthetized with isoflurane for imaging experiments. Each breathing cycle consisted of an inhalation of hyperpolarized ^{3}He/^{4}He gas mixture, a brief breath hold for image acquisition, further inhalation of pure O_2, and then passive exhalation. A 2D diffusion-weighted gradient-echo sequence was used to acquire 5, 2-mm thick image-slices with a field of view 4 × 4 cm and 64 × 64 imaging matrix (b = 0, 1, 2, 4, 6, 9 s/cm^2, diffusion time is 440 μs). In most cases images were also acquired with 10 b-values to test reliability and robustness of fit. All imaging was performed on an Oxford 4.7 T horizontal-bore magnet. A custom-built double resonance coil tuned to both ^{3}He and ^{1}H frequencies was used. An established mathematical model[4] was fitted to the multi-b ^{3}He diffusion-weighted images on a voxel-by-voxel basis using Bayesian analysis software. This generates parametric maps including alveolar depth h, acinar airway radius R (Figure 1) and the mean linear intercept (Lm). To validate MRI-based measurements, quantitative histology was conducted to determine Lm.

Results

The signal-to-noise ratio for ^{3}He MR images ranged from 60 (for b = 9) to 170 (for b = 0). The fitting by Bayesian analysis was excellent in each case and the root mean squares of the residues (RMS) were all below 3% of RMS of the original signals. No differences were seen between results of 6- and 10-b-value experiments. Individual morphometric data from imaging, in addition to Lm measured by histology, are summarized in Table 1. Representative parameter maps are shown in Figure 2. For the 7 normal mice studied, the results show very small variation between individual mice and are in good agreement with quantitative histology performed by us and others[7]. The parameters R, h, Lm, N_a, and S/V characterizing mouse lung microstructure are all fairly homogeneous throughout the entire lung, though some regional variation is seen, with slightly elevated R and Lm in the lung periphery. In the two cases where images were acquired at two different lung inflation pressures (3 cm and 22 cm H_2O), R increased by 7 μm and h decreased by 3 μm when imaging at the higher pressure.

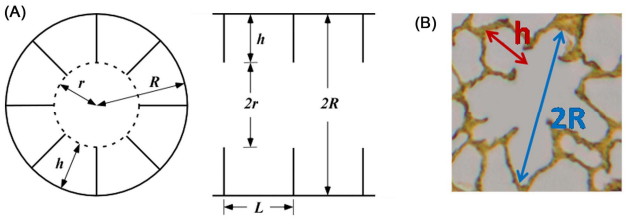

Figure 1 (A) Schematic structure of the model of an alveolar duct shown in 2-D perpendicular and parallel to the long axis of the duct. (B) A typical duct (long axis perpendicular to the image) seen via histology.

Mouse No.	R (μm)	h (μm)	Lm (μm)	N_a (mm^{-3})	S/V (cm^{-1})	Lm (Histology)
1	95.6±7.0	49.8±6.7	61.0±12.5	3920±829	702±88.6	54.5±5.0
2	100.4±6.4	49.2±4.4	66.0±10.2	3360±632	642±69.1	52.8±5.6
3	97.4±7.9	49.3±6.3	62.4±13.1	3760±854	689±86.7	49.6±5.6
4	94.7±6.7	51.3±5.9	58.7±11.6	4020±784	722±87.9	52.7±4.5
5	92.0±6.4	52.9±3.6	54.6±10.1	4390±871	762±105.0	50.6±3.4
6	103.3±5.8	58.3±3.9	60.1±8.8	3680±536	682±70.2	-
7	96.7±5.9	51.4±4.2	60.1±8.4	3760±670	688±82.4	-
Mean	97.2	51.7	60.5	3840	698	52.0
Std Dev	3.7	3.2	3.5	3920±829	702±88.6	1.9

Table 1 Summary of morphometric parameters obtained via ^{3}He MRI from 7 normal mice, with histological comparison (right column)

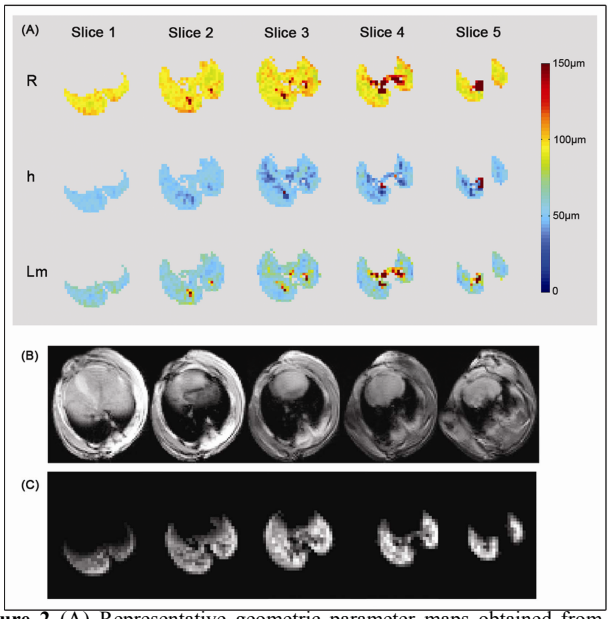

Figure 2 (A) Representative geometric parameter maps obtained from one normal mouse lung. (B) Corresponding ^{1}H images showing the anatomical positions. (C) Corresponding HP ^{3}He ventilation images (b=0).

Conclusions: Here we demonstrate for the first time images of *in-vivo* morphometry in the mouse lung via hyperpolarized ^{3}He diffusion MRI. This technique allows us to measure the same physiological parameters as in microscopic histology (Lm, S/V, N_a), but noninvasively and with tomographic information at microscopic length-scales. Precise quantification of microstructure in normal mouse lung by ^{3}He diffusion MRI opens up exciting possibilities for exploring structural changes at the alveolar level in a broad range of mouse pulmonary disease models, both longitudinally and with precise spatial localization and repeatability. Such promising attributes are likely to make ^{3}He lung morphometry a valuable tool for drug discovery and in understanding longitudinal and spatially-localized changes in individual animals.

References

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