Assessment of In-vitro Lung Structure using Hyperpolarized He-3 ADC MRI: Comparison with In-vivo Measurements and Repeatability

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Introduction: In-vivo studies with hyperpolarized helium-3 (He-3) gas are expensive and time-consuming, and thus are often not justified to test new MR pulse sequences. The use of an appropriately preserved small-animal lung would be ideal since no support staff (e.g., nurse or veterinary technologist) are required to perform the study and only a very small amount of hyperpolarized gas is required, both of which decrease the cost. Glass beads have been used as a hyperpolarized-gas diffusion phantom, but this approach has limitations for lung imaging applications, including the shape and connectivity of the airspaces and the large susceptibility-induced gradients at the surface of the beads. In this study, He-3 apparent diffusion coefficient (ADC) measurements were performed in four rabbits, first in-vivo and then in-vitro, after appropriately preserving the lungs. The preserved lungs from a fifth rabbit were used to assess the repeatability of the ADC measurements and to verify the microstructural integrity of the lung with histology.

Methods and Materials: Five New Zealand rabbits were used in this study, one for repeatability and histology, and four for in-vivo/in-vitro comparison of ADC measurements. All animals for the in-vivo/in-vitro comparisons were imaged less than a week prior to being sacrificed. Lungs were harvested in block and dehydrated with dry compressed air for 72 hours at a pressure of 30cm H_2O (Figure 1, left). For the in-vitro imaging, the lungs were flushed multiple times with nitrogen gas, prior to being injected with He-3 and imaged using the same sequence and parameters as those used in-vivo (Figure 1, center and right). All studies were performed on a 1.5 Tesla whole-body MR scanner (Magnetom Sonata, Siemens Medical Solutions, Malvern, PA) using a flexible radio-frequency RF coil (IGC Medical Advances, Milwaukee, WI) tuned to the He-3 frequency. A FLASH-based pulse sequence with bipolar gradients for diffusion sensitization was used with *b*-value pairs of b=0, 4 s/cm^2 and b=0, 1.6 s/cm^2. Two (in-vitro) or three (in-vivo) contiguous image slices were acquired in order to cover the entire lung; slice thickness 20 mm (in-vivo) or 30mm (in-vitro); matrix size 64x128; in-plane resolution 2.2 x 2.2 mm^2; TR/TE 12/6.8 ms; FA 8°. For the repeatability measurements, the same sequence and parameters were repeated in two different studies (Figure 2). For the in-vivo studies the animals received 50cc of He-3 per inhalation during a single breath-hold. For the in-vitro studies 30cc of He-3 were used per measurement. Multiple tissue samples were removed from one lung set and prepared for histology slides (Figure 3). These samples were cut with a manual microtome in 5μm thick slices, after being embedded in paraffin.

Results: Figure 2 shows in-vitro ADC maps from the same preserved lung, measured with two separate injections of He-3 in two different studies, but with the same pulse sequence and parameters. The difference between the mean ADCs for the two measurements (0.156 cm^2/s and 0.161 cm^2/s for the first and second measurements, respectively) was only 3%, and the histograms and ADC maps were very similar (Figure 2). The histological images verified that the lung microstructure was preserved during the drying process (Figure 3). The difference between the mean ADC values from the in-vitro and in-vivo measurements in the four lungs were: 3.6%, -1.7%, -5.3%, -7.2%. For three of the four cases, the ADC values were slightly smaller for the in-vitro measurements.

Discussion: We demonstrated the successful creation of a preserved animal lung model capable of being used in multiple in-vitro diffusion measurements in a highly repeatable fashion. The overall mean ADC values obtained in-vitro were similar to the corresponding in-vivo mean ADC values obtained from the same animal, with absolute differences no more than 7.2%. The fact that ADC values were typically slightly smaller for the in-vitro measurements suggests that the degree of alveolar expansion during the drying process was close to, but slightly less than, that during the in-vivo breath-holds. Similar lungs preserved more than 12 months ago have not shown signs of degradation and have been used for histological and morphometric measurements.

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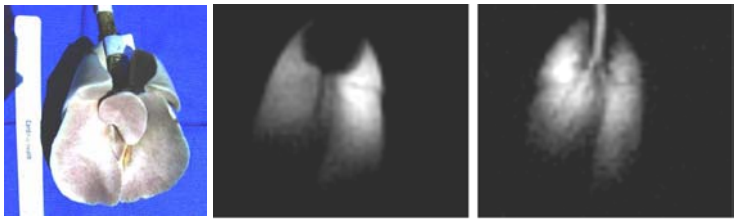

Figure 1 – Left, photograph of a preserved rabbit lung. Right, two contiguous in-vitro He-3 ventilation images (b=0 s/cm^2) from the lung set on the left.

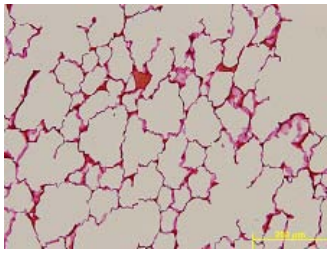

Figure 3 – Histological digital image acquired from a tissue sample from a preserved lung, showing the microstructural integrity after the drying process. Magnification = 10x.

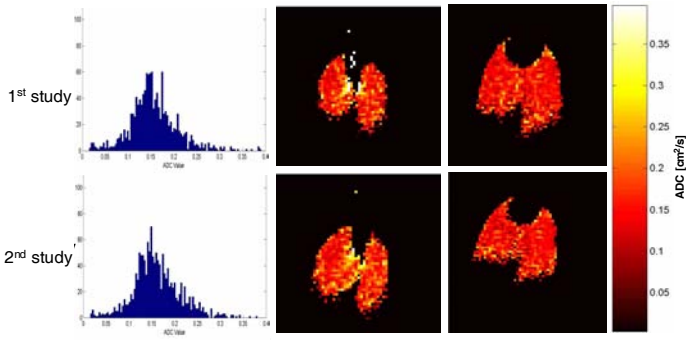

Figure 2 – In-vitro He-3 ADC repeatability. ADC maps and the histogram shown in each row are from separate studies. The overall mean ADC/STD values from the 1st and 2nd studies were 0.156/0.052 cm^2/s and 0.161/0.051 cm^2/s, respectively.