Short- and Long-range Diffusivities of ^{3}He in Healthy and Emphysematous, Excised Human Lungs

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INTRODUCTION: Measurements of ^{3}He diffusion over long times and distances (3-10 s and 3 cm) are possible with spatially modulated longitudinal magnetization [1] and may offer a sensitivity advantage over the short-range diffusion (2-8 ms and 0.5 mm) [2]. The spatially-resolved diffusivity may be determined from the decay rate of the fractional depth of the longitudinal modulation [2]. In normal lung, to traverse centimeter distances gas must diffuse along the network of branching airways, climbing up and down several airway levels; in emphysematous lung collateral pathways allow the gas to find more direct routes to diffuse between distant points, and D_{sec} is increased [2,3]. The ratio of surface area to volume (SA/V) in lung is an accepted measure of the extent and severity of emphysema [4] and is compared here to the restricted diffusivities of ^{3}He to assess these as noninvasive measures of emphysema.

MATERIALS AND METHODS: Six lungs with severe emphysema were removed at transplant and stored at 40°F under saline bath for 2-5 days. One healthy donor lung, rejected for transplant for technical reasons, was stored similarly. All lungs were sealed of leaks, thoroughly depleted of O_2 with N_2 purge, and inflated to functional residual capacity before instillation of 300 mL of hyperpolarized ^{3}He via gas syringe. After 6-8 rebreathing strokes to homogenize the gas distribution, magnetization tagging was performed at inspiration, and repeated FLASH imaging followed (FA = 3°) for inspection of the modulated magnetization, with images in approximately sagittal planes. After imaging the lungs were frozen at constant volume, sliced into transverse sections, and sampled extensively with a cork-borer for histological measurements (14-19 samples per lung). Later the samples were fixed in cold alcohol, warmed, and processed into paraffin. SA/V was measured in a 20-µm slice of each section using an accepted technique [4].

Hyperpolarized ^{3}He of polarization 40% was prepared with two homebuilt and one commercial polarizer (Amersham Health). A solenoid rf coil with high sensitivity (Q=80) was used at 48.47 MHz with a Siemens Magnetom Vision. Sinusoidal modulation of wavelength 3 cm was effected in axial planes by two 45° rf pulses separated by a gradient pulse. The 20-mm thick slices were 320-mm FOV, with 5 mm x 2.5 mm pixels. Maps of D_{sec} were generated through the decay of the fractional modulation calculated from neighboring pixels over one wavelength [2].

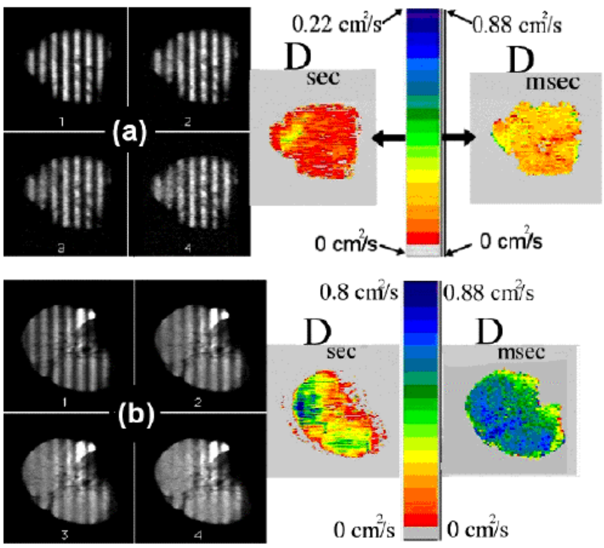

Figure 1: In (a) each grayscale image of this healthy lung advances 1.96 s (the first being immediately after initial tagging pulses). Little decay of modulation is evident, and the resultant map of D_{sec} has an average of 0.017 cm²/s, about 12x smaller than D_{msec}. In (b) each grayscale image advances only 0.38s; decay is apparent beginning at image #2. D_{sec} approaches D_o in the apex—an increase of 50 times over healthy lung.

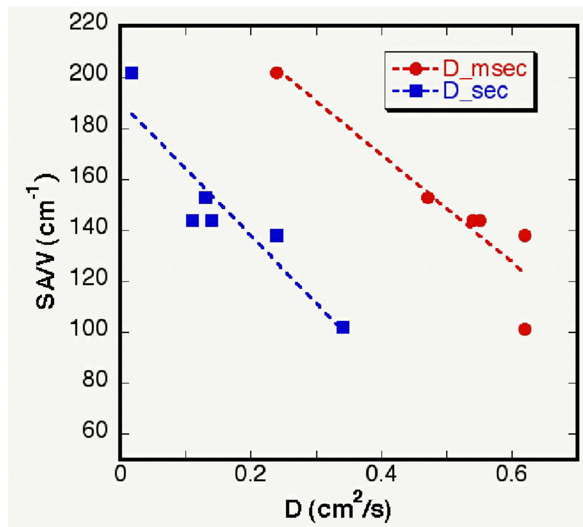

Figure 2: Comparison of histology (SA/V) to D_{sec} and D_{msec} of ^{3}He in six cases where reliable data existed for all three measurements. Data are averaged over samples of the entire lungs. While D_{sec} has a much larger fractional increase, both diffusivities show inverse relationships with SA/V. The relationship is not expected to be linear; dashed lines are therefore only meant as guides to the eye.

RESULTS: Images had very high SNR (typically 100 or higher), despite the small tip angle, because of the absence of saline in the lung tissue. T_1 was long (between 7 and 9 minutes) indicating that virtually all O_2 had been removed. Near-complete modulation (minima < 10% of the maxima) was realized in almost all cases. The nominally healthy lung had very restricted long-range diffusion ($\langle D_{sec} \rangle$ = 0.017 cm²/s) in nearly all parts of the 4 slices imaged, which covered most of the lung (Figure 1(a) presents one slice). The resultant map of D_{sec} reports low and uniform values, save in the apex (at left) where the enhanced D_{sec} may evidence the donor's smoking history. A map of the short-range diffusivity D_{msec} shows no increase in the same area.

The average diffusivity D_{sec} measured in emphysematous lungs was 0.19 cm²/s—an increase by a factor of about 11 from that of the healthy lung. In nearly every case there was marked heterogeneity of D_{sec} compared to the healthy lung, with many regions of greatly enhanced diffusion (D_{sec} > 0.3 cm²/s), particularly in the upper lobes. Some regions with D_{sec} near the unrestricted value were also detected, representing a diffusivity increase over normal lung by a factor of about 50. In addition, D_{sec} reveals significant regional differences in lungs with nearly uniform, unrestricted values of short-range diffusivity, D_{msec} (Figure 1).

Histology revealed lower SA/V in emphysematous lungs (131 ± 38 cm^{-1}, the average over six lungs) than in the healthy lung (200 ± 32 cm^{-1}). Comparison of SA/V to D_{msec} (0.58 ± 0.14 vs. 0.24 ± 0.07 cm²/s, emphysema vs. healthy) showed an inverse relationship, as did comparison of histology to D_{sec} (Figure 2).

CONCLUSIONS: Hyperpolarized ^{3}He MRI in excised human lungs takes advantage of the high spin sensitivity and uniform gas distribution that can be produced by rebreathing, even in the most diseased regions of lung. The measurements of D_{sec} provide very large contrast between healthy and severely emphysematous lung, with emphysematous increases as large as a factor of 50 (compared to a factor of 4 for D_{msec}). D_{sec} also has the potential to be more sensitive to small, initial changes in lung structure, as suggested by the measurements in the donor lung. Measurements of D_{sec} may be useful for characterizing the collateral ventilation pathways that become important in emphysema. Both measurements of ^{3}He diffusion correlate to changes in SA/V; restricted ^{3}He diffusion is thus shown for the first time to relate directly to histologic changes associated with emphysema in humans.

REFERENCES: [1] Owers-Bradley JR, *et al.*, *Proc 10th ISMRM 2002*, 2016. [2] Leawoods JC, *et al.*, *Proc 11th ISMRM 2003*, 512. [3] Macklem PT, *New Engl J Med* 1978; 298: 49. [4] Thurlbeck WM, *Thorax* 1967; 22: 483. **ACKNOWLEDGMENTS:** This research was supported by NIH grants R01HL070037 and R01HL62194.