Acinar Structural Changes in Mild COPD Detected By In Vivo Lung Morphometry With Hyperpolarized Helium-3 MRI

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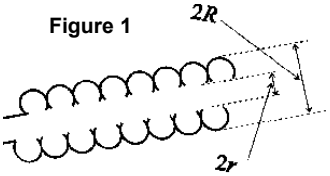
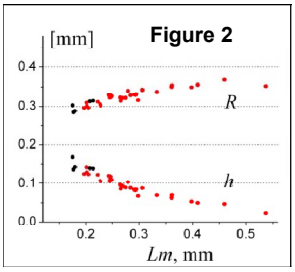
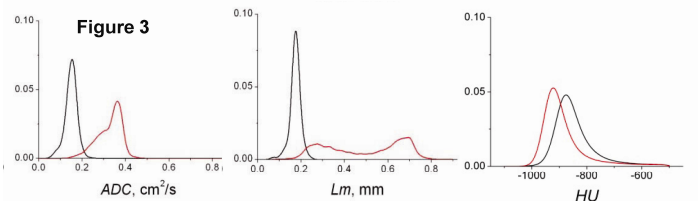
Hyperpolarized ^{3}He diffusion MRI is increasingly becoming the non-invasive standard for measuring regional pulmonary changes in COPD. However, it is unclear what lung microstructural features are reflected in the commonly utilized measurements of ^{3}He ADC. To surmount this limitation, we utilize a model-based approach that treats the acini of the lung (where 95% of gas resides) as a network of cylindrical airways lined with alveoli (alveolar sleeves) [1], shown schematically in Figure 1. Based on this structure, there should be distinct diffusivity values for motion along and across the airways [2]. By modeling this diffusion anisotropy, we can estimate acinar geometric parameters, such as the airway internal (*r*) and external (*R*) radii and alveolar depth (*h*=*R*-*r*) [3,4]. From these results, the model also allows local estimation of lung surface-to-volume ratio (*S/V*), number of alveoli per unit lung volume (*Na*), and mean linear intercept (*Lm*) - parameters that have been used by lung physiologists for decades and are accepted as established markers of emphysema [4]. The mean linear intercept evaluated in this manner has been validated against the histological mean linear intercept [4]. Thus, this approach provides the basis for *in vivo* lung morphometry, opening the door to studies of structural changes in the lung without utilizing lung biopsy.



Materials and Methods: Thirty subjects with significant smoking histories (red symbols in Figure 2, 50 ± 20 pack years, average age 62 ± 3 years, 26 @ GOLD 0, 3 @ GOLD 1, 1 @ GOLD 2) were recruited for hyperpolarized helium-3 MRI from the National Lung Screening Trial (NLST), along with five never-smoking subjects (black symbols in Figure 2). In the NLST, subjects received a multi-slice axial low-dose chest CT examination on a Siemens Sensation 16 (Siemens Medical Systems, Iselin, NJ) (0.633 x 0.633 x 2 mm resolution) within one year prior to the MRI examination. All procedures were performed with IRB approval and a ^{3}He IND FDA exemption. A complete pulmonary function test was performed on the day of helium imaging for each subject. Helium diffusion studies were conducted on a 1.5 T Siemens Sonata using a custom-built ^{3}He volume transmit / 8-channel receiver pair (Stark Contrast MRI Coils Research, Erlangen, Germany). Hyperpolarized ^{3}He gas was prepared using spin-exchange optical pumping on either a home-built apparatus or a commercial IGI.9600.He polarizer (General Electric, Fairfield, CT). After practicing breathing maneuvers with room air during proton scout imaging, the subjects exhaled to functional residual capacity and inhaled 0.6 liters of hyperpolarized ^{3}He gas mixed with 0.4 liters of nitrogen. Axial 2D multi-slice diffusion-weighted ^{3}He FLASH images were acquired during a nine-second breath-hold (128 x 64; resolution = 7 x 7 x 30 mm; TR/TE = 13/8.32 ms; diffusion time = 1.8 ms; 3 slices; b-values = 0, 2, 4, 6, 8, 10 s/cm^2). The ^{3}He MRI images from each channel of the receiver coil were individually phased [5,6] and the real data was jointly analyzed utilizing Bayesian probability theory [7] .



Results: Figure 2 plots the mean external airway radius (*R*) and the alveolar depth (*h*) for these subjects as a function of the mean linear intercept (*Lm*) derived from the helium diffusion signal. These results demonstrate that in the initial stages of emphysema, as *Lm* increases, there is a significant decrease in alveolar depth (*h*). At the same time, the airway radius (*R*) grows substantially with emphysema progression, reflecting tissue inflation and alveolar destruction and coalescence. The mechanism of "dilation of alveolar ducts with retraction of alveolar walls" was first suggested decades ago to describe microscopic manifestation of emphysema in human lungs [8] and was later confirmed in humans [9] and rodents [10,11]. Our results are the first non-invasive observation of this phenomenon and allow regional quantitation of such changes with emphysema progression.



As COPD is known to be a heterogeneous disease, we have also examined the distribution of parameter values for each subject. Figure 3 shows histograms of parameter values across the lungs for a normal (black) and COPD subject (red). While the CT for these subjects (obtained through the NLST) shows a shift towards decreased tissue density (smaller HU), the shift in the helium diffusion measurements is significantly larger. Most interesting is that *Lm* demonstrates a pronounced "bipolar" feature that is only hinted in ADC and is not seen in CT data at all. This "bipolar" pattern illustrates that disease severities can vary significantly across the lung, and are easily missed by global measurements (e.g. PFT) and random biopsy samples.

Conclusions: Non-invasive in vivo lung morphometry with hyperpolarized helium-3 MRI is a sensitive method for detecting early emphysema and provides unique insights into changes in the acinar microstructure, previously only attainable for localized regions through invasive biopsy. This technique detects significant disease heterogeneity across the lung and analysis of these patterns can provide important insights into disease phenotypes and for monitoring disease progression and regression.

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References: [1] Haefeli-Bleuer B, Anat Rec 1988;220(4):401-414. [2] Yablonskiy DA, Proc Natl Acad Sci U S A 2002;99(5):3111-3116. [3] Sukstanskii AL, J Magn Reson 2008;190(2):200-210. [4] Yablonskiy DA, J Appl Physiol 2009;107(4):1258-1265. [5] Bretthorst GL, Journal of Magnetic Resonance 2008;191:184-192. [6] Bretthorst GL, Journal of Magnetic Resonance 2008;191:193-201. [7] Quirk JD, J Magn Reson 2009;198(1):49-56. [8] Hartroft WS, Am J Pathol 1945;21:889-903. [9] Finlay GA, Am J Pathol 1996;149(4):1405-1415. [10] Kuhn C, 3rd, Lab Invest 1976;34(1):2-9. [11] Morris SM, Anat Rec 1981;201(3):523-535.