Hyperpolarized ^{129}Xe Diffusion MRI of the Lungs in Healthy Subjects and Chronic Obstructive Pulmonary Disease Patients

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Introduction: Chronic obstructive pulmonary disease (COPD), which often involves destruction of alveolar microstructure, is a progressive, potentially terminal illness and is the 4th leading cause of chronic morbidity and mortality in the US **[1]**. COPD-related changes in alveolar microstructure can be visualized using diffusion weighted hyperpolarized (HP) ^{3}He MRI as an alternative to Computed Tomography (CT) **[2]**. Unfortunately, escalating costs and increasing scarcity have prohibited the widespread use of HP ^{3}He, and it has been suggested that ^{129}Xe, which is readily available, may also be suitable for diagnostic ADC weighted MRI. While ^{129}Xe ADC imaging has previously been demonstrated in healthy human volunteers **[4]** and has been shown to be sensitive to microstructural changes in animal studies **[3]**, it has not yet been reported in patients with disease. In this work we investigated the potential utility of ^{129}Xe ADC MRI in both healthy volunteers and COPD patients.

Methods: ^{129}Xe gas was polarized by Rb vapor spin exchange using a prototype commercial polarizer (GE Healthcare, Durham, NC). ADC images were obtained from both healthy volunteers (N=6) and COPD patients (N=6) (some patients had no evidence of emphysema on a CT scan) using a 1.5 T GE scanner with a EXCITE 14M5 platform. (FOV=40 cm, matrix = 64×64, ten 15 mm slices, BW = 15.6 kHz, TE/TR = 9.3/12 ms, $\alpha = 5.1°$, and b=12 s/cm^2). The gradient amplitude was 3.2 G/cm with a ramp time of 500 µs and a pulse width of 2.4 ms. Studies were conducted under the GE Healthcare IND and were approved by the Duke University Medical Center IRB as part of a Phase 1 clinical trial conducted by GE Healthcare. Subjects inhaled 1 L of polarized ^{129}Xe (83% isotopically enriched) and, for a given slice, the image acquisitions were interleaved **[5]**. ADC maps were generated in MATLAB™. Background noise was suppressed by generating a binary mask for each image slice, with the threshold=mean+2×std of a 200x50 region in the background. The mask was eroded and dilated with a circular structuring element with a 3 pixel radius to remove the discontinuous noise from background. ADC values were calculated for each pixel by log-linear fitting of the signal intensities. The airways were manually segmented in MATLAB™, and the ADC values for the airways and parenchyma were calculated separately.

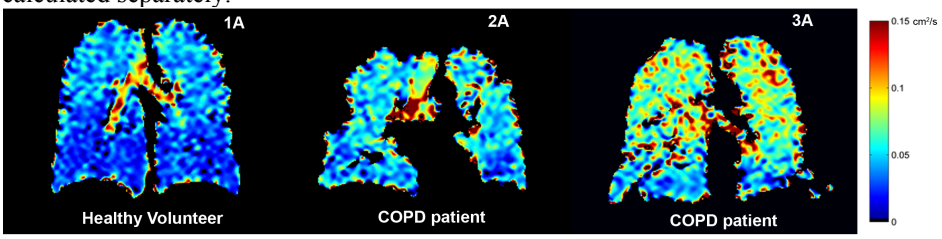

Fig 1-3A: Representative slices from ADC maps. **1A-** Low ADC values in parenchyma reflect restricted diffusion. Higher ADC in airways results from reduced confinement. **2A-** Mildly elevated ADCs suggest some destruction of alveolar microstructure. **3A-** Significantly elevated ADC for the entire lung.

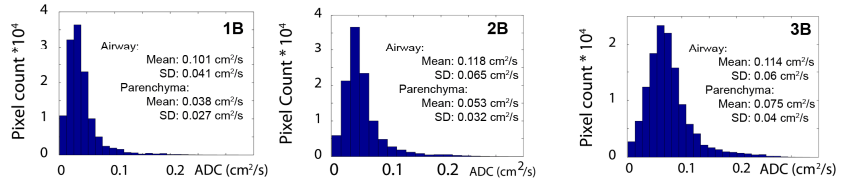

Fig 1-3B: Histograms of the entire volume corresponding to F**ig 1-3A**. **1B -** A homogenous distribution of ADCs. Increasingly wider ADC distribution for COPD patients are seen in 2B and 3B.

Results and Discussion: For all healthy volunteers, the pooled mean parenchyma ADC was 0.036±0.003 cm^2/s but was significantly elevated ($p<0.007$) in COPD patients to 0.058 ±0.014 cm^2/s, which is comparable to the xenon self diffusion coefficient of 0.06 cm^2/s **[6]**. The larger ADC values in the COPD patients are indicative of alveolar destruction and qualitatively, are consistent with CT data in the same subjects. In contrast, mean airway ADC values of 0.091 ±0.009 cm^2/s and 0.112±0.029 cm^2/s were similar for healthy subjects and COPD patients, respectively, consistent with absence of xenon confinement. ADC values that exceed the self diffusion coefficient of xenon are observed in the airways of both groups and in the parenchyma of COPD patients. This increase beyond the self diffusion value results from xenon dilution by lighter pulmonary gases, and is expected to reach a maximum value of 0.15 cm^2/s at sufficiently high dilution **[7]**. Higher ADC values are also seen from COPD patients in the superior lobes of the lung, which qualitatively agrees with ^{3}He ADC trends observed in smokers **[2]**. In addition to larger mean ADC values, individual COPD patients exhibit a greater heterogeneity of ADC values within the lung.

Conclusions: We demonstrate that HP ^{129}Xe ADC measurements are sufficiently sensitive to pulmonary microstructure to differentiate between healthy volunteers and COPD patients with early stage emphysema. The ^{129}Xe ADC is also strongly influenced by the gas composition within the alveoli. Further work is required to completely elucidate the relative contribution of confinement and gas composition to the observed ADC values. While the interpretation of ^{129}Xe ADC may be complicated by the effects of gas dilution, these same dilution effects may provide a novel opportunity to examine gas mixing at the alveolar level.

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