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Emphysematous changes and normal variation in smokers and COPD patients using diffusion ^{3}He MRI

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Abstract

Introduction: This study aims to quantify global and regional changes of diffusive motion of ^{3}He gas within the lung, as determined by hyperpolarized ^{3}He MR apparent diffusion coefficient (ADC) measurement, in non-smokers, smokers and chronic obstructive pulmonary disease (COPD) patients.
Methods: Age-matched groups of six healthy non-smokers, five healthy smokers and five patients with COPD. The experiments were performed with approval from the local Research Ethics Committee. Diffusion imaging was performed following hyperpolarized ^{3}He gas inhalation, producing ADC maps. Mean and standard deviation of the ADCs were used to compare the subject groups and assess regional variations within individuals.
Results: The intra-individual standard deviation of ADC in the healthy smokers was significantly larger than that of the non-smoking group ($P < 0.02$). Compared to the non-smoking group, COPD patients had significantly higher mean and standard deviation of ADC ($P < 0.01$). The mean ADC in the anterior half of the chest was systematically higher than in the posterior half in the healthy non-smoking subject group.
Discussion: This study suggests that there are regional trends in the ADC values of healthy volunteers that may have implications for the clinical interpretation of ADC values. Less homogeneous ADC values have been detected in asymptomatic smokers, indicative of damage to the distal air spaces.

Keywords: Chronic obstructive pulmonary diseases (COPD); Emphysema; Smoking; ^{3}He; MRI; Apparent diffusion coefficient (ADC)

1. Introduction

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the world and is increasing in prevalence [1]. Until now, clinical imaging of the lung parenchyma has been performed with techniques such as chest radiography and X-ray computed tomography. The chest radiograph can detect extensive bullous disease, however, CT has been shown to be more sensitive [2,3], and is a well-established modality and is currently the technique of choice for assessing the extent and distribution of emphysema. These techniques have their shortfalls, the CXR has limitations in sensitivity, and they both involve the use of ionising radiation. The recent introduction of MR imaging with noble gases means that the lung air spaces can be evaluated without exposure to radiation. This new approach to ventilation imaging with MR has been developed during the past 7 years by using the ^{3}He gas as an inhaled MR contrast agent [4,5]. Performing a ^{3}He MRI scan involves inhalation of ^{3}He followed by immediate scanning of the subject. A laser is used to induce an extremely large non-equilibrium nuclear polarization in the ^{3}He atoms before they are administered to the subject. The level of nuclear polarization that can be achieved with this non-equilibrium technique is

Abbreviations: ADC, apparent diffusion coefficient; FEV_1, forced expiratory volume in 1 s; FEV_1/FVC, FEV_1/forced vital capacity; FRC, functional residual capacity; SNR, signal-to-noise ratio

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more than 100,000 times the typical level of polarization that is produced with conventional equilibrium techniques. The resulting increase in signal strength is more than enough to compensate for the low density of the gas and allows direct visualization of the gas and its distribution in the lung by using MR techniques.

The apparent diffusion coefficient (ADC) of hyperpolarized ^{3}He has been measured in healthy and diseased lungs. It has been shown that ADC values are increased in emphysema, likely to be due to the disruption of the lung parenchyma resulting in alveolar destruction and enlargement [6,7]. This study aims to explore the application of ^{3}He diffusion MRI in the determination of regional and global ADC variation in healthy non-smokers, smokers and COPD patients.

2. Methods

Subjects were recruited through open poster advertisement in the radiology and respiratory medicine clinics. Healthy controls were defined, as never smokers, having no previous history of chest diseases and without chest symptoms at the time of MRI scan. Healthy smokers were defined as current smokers with a smoking history of more than 10 pack years, but without a history of chest disease or chest symptoms at the time of MRI scan and normal spirometric indices. Smokers with proven COPD were those subjects that had a smoking history of more than 10 pack years, with airway symptoms and abnormal spirometry according to the GOLD guidelines [8]. Six healthy non-smokers with a mean age of 52 years (range 48–63 years), five healthy smokers with a mean age of 54 years (range 51–58 years) and five subjects with smoking related COPD with a mean age of 53 years (range 54–62 years) were enrolled into the study. The experiments were performed with approval from the local Research Ethics Committee. Written informed consent was obtained from each subject prior to enrolment.

All work was conducted with a 1.5 T whole body MRI system (Eclipse, Philips Medical Systems, Cleveland, OH). The system was equipped with an actively shielded gradient set with a maximum strength of 27 mT/m and a rise time to maximum of 350 μs. The system was custom fitted with a second set of radiofrequency (RF) amplifiers (2 kW, Analogic Corporation, Peabody, MA) and transmit–receive circuits to facilitate resonance at 48 MHz for ^{3}He. A flexible twin saddle quadrature transmit–receive coil was used for all of the ^{3}He work (IGC Medical Advances, Milwaukee, WI). ^{3}He gas was polarized on site by optical pumping with a rubidium spin exchange apparatus (Amersham Health, Durham, NC).

2.1. Dose and delivery

All imaging was performed following inhalation of approximately 300 ml ^{3}He/700 ml N_2 mixture from a Tedlar bag (Jensen Inert Products, Coral Springs, FL) based upon the work of the University of Virginia [9]. The procedure involved the subject performing a 15 s breath hold of ^{3}He gas at inspiration whilst the scanner simultaneously collected the data. A nurse monitored the subject's heart rate, blood pressure and oxygen saturation during the studies using Maglife MR compatible monitoring equipment (Maglife, Bruker, Wissembourg, France) during the session, and a physician (a radiologist and/or an anaesthetist) was present.

2.2. MR methods

^{1}H MRI Single Shot Fast Spin Echo (SS-FSE) imaging was performed at inspiration for anatomical localisation of the lung immediately before ^{3}He MRI. The sequence parameters were: TE, 3.6 ms (minimum); echo spacing, 4.5 ms; slices, 19; slice thickness, 10 mm; order, interleaved; gap, none; matrix, 256 × 128–256; FOV, 42–50.

The ^{3}He ADC imaging took place at full inspiration. The ADC map corresponding to each coronal slice was calculated from two ^{3}He 2D gradient echo images that were obtained with different diffusion-sensitisations. For each phase encode step, the two sequences were interleaved. The two interleaved pulse sequences were identical except that a bipolar diffusion gradient waveform was included on the slice-select axis for the diffusion-weighted scan. This trapezoidal bipolar waveform had a gradient strength of 26 mT/m, ramp up time of 500 μs, a flat (steady-value) time of 460 μs, and a ramp down time of 500 μs. This waveform achieves a *b* value of 2.86 s/cm^2.

The remaining sequence parameters for the diffusion imaging were as follows: TR, 8.5 ms; TE, 6 ms; flip angle, 7°; oriented coronally and acquired sequentially from anterior to posterior; 96 phase encodes with centric ordering, 128 samples; FOV 47 × 29 cm; 9 slices, 15 mm slice thickness, 5 mm slice gap. The total imaging time was 15 s.

The ADC maps were calculated by linear least squares fitting the natural log of the signal intensity versus the *b* value on a pixel-by-pixel basis, using a *b* value of zero for the reference scan. Before calculation of the ADC values, any pixel location whose intensity was less than three times the standard deviation of the background noise in either of the two images was set to zero. All image-processing calculations were done using in-house MATLAB (Mathworks, Natick, MA, USA) code.

2.3. MR imaging data analysis

The subject's ADC maps were assessed in random order by a trained observer who was blinded to the clinical and spirometry data. For each calculated ADC image, histograms of the ADCs were created, and the mean and SD of the ADCs were calculated. The images were analysed using manually segmented region of interest measurements, the whole lung was used in the analysis. The trachea and main bronchi were segmented out of image analysis. To assess regional variations in ADCs between the upper and lower portions of each