Hyperpolarized 3He Magnetic Resonance Imaging ADC Gradients in Healthy Elderly Never-Smokers

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Target Audience: Scientists interested in hyperpolarized gas magnetic resonance imaging (MRI) of the aging lung

Purpose: Previous work has shown a relationship between age and hyperpolarized [3]He MRI apparent diffusion coefficients (ADC) suggesting that there are changes in the lung microstructure that increase alveolar volume during the aging process. However, it is unknown whether these changes in the ADC gradients in the superior-inferior (SI) and anterior-posterior (AP) direction also occur during the aging process. Previous studies have demonstrated that [3]He ADC anterior-posterior gradients were significantly reduced in chronic obstructive pulmonary disease (1), and this was thought to be attributed to regional gas trapping. [3]He ADC anterior-posterior gradients were also shown to normalize in COPD following salbutamol administration-consistent with the relief of regional gas trapping (2). We hypothesized that the anterior-posterior gradient is reduced during the aging process and that there is a significant relationship between the anterior-posterior gradient and age. Therefore, our objective was to quantitatively evaluate the anatomical distribution of ADC using hyperpolarized [3]He MRI in healthy elderly never-smokers.

Methods:

Subjects: Healthy elderly never-smokers ($\leq$ 1 pack year smoking history) between 60-90 years of age with no history of acute or chronic respiratory diseases provided written informed consent to the study protocol approved by the local research ethics board and Health Canada. All subjects underwent spirometry, cycle ergometry, and hyperpolarized [3]He MRI at a single study visit.

Image Acquisition: Imaging was performed on a whole body 3.0 Tesla Discovery 750MR (General Electric Health Care, Milwaukee, WI) with broadband imaging capability as previously described (1). For [3]He MRI, a polarizer system (HeliSpin™) was used to polarize [3]He gas. Hyperpolarized [3]He MRI diffusion weighted images were acquired during breath-hold of a 1L [3]He/N_2 mixture obtained using a fast gradient-recalled echo method (FGRE). Two interleaved images (14s total data acquisition, TR/TE/flip angle = 7.6 ms/3.7 ms/8°, FOV = 40 x 40 cm, matrix 128 x 128, 8 slices, 30 mm slice thickness), with and without additional diffusion sensitization (G = 1.94 G/cm, rise and fall time = 0.5 ms, gradient duration = 0.46 ms, Δ = 1.46 ms, b = 1.6 s/cm^2), were acquired.

Image Analysis: Anatomical differences in ADC were quantified in the five centermost slices by: 1) calculating the absolute ADC difference for AP slices (ΔAP) and SI ROI (ΔSI); and 2) measuring the ADC gradient for AP slices (AP-gradient) and for SI ROI (SI-gradient) in cm^2/second/cm. AP-gradient was defined as the slope of the line that described the change in ADC as a function of distance in centimeters over the five central slices and was calculated using the mean ADC of whole lung slices. The SI-gradient was defined as the slope of the line that described the change in ADC over the upper, middle, and lower ROIs in the five center-most slices. AP-gradient and SI-gradient were obtained from the slope of five points and three points, respectively, using linear regression. We also evaluated relationships between ADC gradients and spirometry measurements and age.

Statistical Analysis: Linear regression (r^2) and Pearson correlation coefficients (r) were used to determine the relationships between lung anatomical position and [3]He ADC measurements. All statistical analysis was performed using GraphPad Prism version 4.00 (GraphPad Software Inc, San Diego, CA, USA), results were considered statistically significant when the probability of making a Type I error was less than 5% ($p < 0.05$).

Results: Table 1 shows mean subject demographic characteristics, spirometry measurements, and [3]He ADC measurements for thirty-five healthy elderly never-smokers. The mean ADC ΔAP and ΔSI were 0.05 ± 0.03 cm^2/second and 0.017 ± 0.017 cm^2/second, respectively. The mean AP-gradient and SI-gradient were -0.013 ± 0.008 cm^2/second/cm and -0.002 ± 0.012 cm^2/second/cm, respectively. The [3]He ADC anterior-posterior gradient was statistically significant (r = -0.96, r^2 = 0.92, p = 0.009) (Figure 1A), but the [3]He ADC superior-to-inferior gradient was not significant (r = 0.3, r^2 = 0.1, p = 0.8) (Figure 1B). The ratio of residual volume (RV) to total lung capacity (TLC) correlated significantly with the AP-gradient (r = 0.37, p = 0.03) (Figure 1D). There was no statistically significant relationship between age and ADC gradients (Figure 1C).

Discussion: There was a significant decrease in mean ADC from the most anterior and posterior slices of the lung as expressed as ΔAP and AP-gradient due to compressible airspaces in healthy elderly never-smokers. AP ADC gradients were significantly correlated with RV/TLC which suggests regional gas trapping occurs in the healthy elderly. However, there was no significant correlation between the AP ADC gradients and age suggesting that regional gas trapping does not occur during the aging process for all subjects.

Conclusions: In a group of healthy elderly never-smokers, ADC anatomical differences in the anterior-posterior direction were significant and mean ADC was dependent on anterior-posterior location, but ADC gradients were not dependent on age.

References

1. Evans, A. *et al. J Magn Reson Imaging.* (2007)
2. Kirby, M. *et al. J App Phys.* (2011)

Table 1. Subject demographic characteristics, spirometry and hyperpolarized [3]He ADC measurements of healthy elderly never-smokers

	Healthy Elderly n = 35
Age, yrs (±SD)	71 (6)
Male Sex	17
BMI, kg/m^2 (±SD)	27 (4)
FEV1%$_{pred}$ (±SD)	105 (21)
FVC%$_{pred}$ (±SD)	101 (18)
FEV1/FVC (±SD)	77 (6)
IC%$_{pred}$ (±SD)	103 (21)
RV/TLC%$_{pred}$ (±SD)	100 (18)
DL$_{co}$%$_{pred}$ (±SD)	87 (19)
ADC, cm^2/s (±SD)	0.27 (0.04)
ΔAP, cm^2/s (±SD)	0.05 (0.03)
AP-gradient, cm^2/s/cm (±SD)	-0.013 (0.008)
ΔSI, cm^2/s (±SD)	0.017 (0.017)
SI-gradient, cm^2/s/cm (±SD)	-0.002 (0.012)

BMI = body mass index, FEV$_1$= forced expiratory volume in one second, FVC= forced vital capacity, TLC = total lung capacity, IC= inspiratory capacity, RV = residual volume, DL$_{co}$ = diffusing capacity of the lung for carbon monoxide, ΔAP = change in ADC from the most anterior to the most posterior slice, ΔSI = change in ADC from the most superior to anterior region of interest, SD = standard deviation.
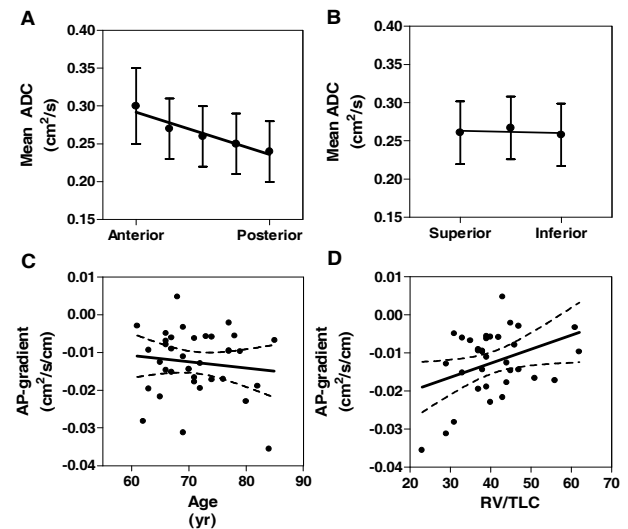
Figure 1. Mean ADC gradients. **A)** Mean [3]He ADC for thirty-five subjects from the anterior to the posterior slices (r = -0.96, r^2 = 0.92, p = 0.009). **B)** Mean [3]He ADC for thirty-five healthy elderly subjects from superior to the inferior ROI (r = 0.3, r^2 = 0.1, p = 0.8). **C)** Linear regression for AP-gradient and age (r = 0.37, r^2 = 0.13, p = 0.03). **D)** Linear regression for AP-gradient and ratio of residual volume to total lung capacity (r = -0.12, r^2 = 0.01, p = 0.45). The error bars represent the standard deviation.