EVALUATION OF SHORT TERM REPRODUCIBILITY OF HYPERPOLARIZED HELIUM-3 MAGNETIC RESONANCE IMAGING OF ADULT CYSTIC FIBROSIS USING A SEMI-AUTOMATED SEGMENTATION TOOL

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Purpose: In the assessment of cystic fibrosis (CF), longitudinal spirometric measurements provide the context for potential changes in lung function over time. With the recent rapid development of a wider array of CF treatment options there is an urgent requirement for precise, practical and sensitive clinical endpoint measures that can be used to determine treatment response and CF disease progression over time. Pulmonary functional imaging using hyperpolarized helium-3 (^{3}He) magnetic resonance imaging (MRI) is advantageous due to its unique ability to potentially evaluate longitudinal and intensive serial studies in young adults without radiation risk. Thus, the objective of this work is to evaluate the short term (7 ± 2 day) reproducibility of hyperpolarized ^{3}He measurements in adults with CF using a semi-automated software tool.

Materials and Methods

Subjects: Twelve subjects with CF provided written informed consent and underwent spirometry, plethysmography and hyperpolarized ^{3}He MRI. CF patients were enrolled between the ages of 18 and 45 years, with baseline $FEV_1 > 50\%_{pred}$ measured by spirometry on the first scanning visit. A 7 ± 2 day scan-rescan test was chosen in order to mimic day-to-day changes common in CF but to exclude longer term alterations in health and lung physiology that accompany CF lung disease progression.

Image Acquisition: MRI was performed immediately after pulmonary function tests, on a whole body 3.0 Tesla Excite 12.0 MRI system (GEHC, Milwaukee, WI USA) with broadband imaging capability as previously described. ^{1}H images were acquired prior to ^{3}He imaging with subjects scanned during a 1L breath-hold of $^4He/N_2$ using the whole body RF coil and proton fast spoiled gradient-echo (16s total data acquisition, relaxation time (TR)/echo time (TE)/flip angle = 4.7 ms/1.2 ms/30^o, field-of-view (FOV) = 40 x 40 cm, matrix 256 x 256, 14 slices, 15 mm slice thickness, 0 cm gap). Prior to ^{3}He MRI, a polarizer system (HeliSpin™, GEHC, Durham, NC), with spin-exchange optical pumping, was used to polarize ^{3}He gas to 30-40 %. Doses (5 mL/kg body weight) were administered in 1 L plastic bags diluted with ultrahigh purity, medical grade nitrogen (Spectra Gases, Alpha, NJ). Polarization of the diluted dose was quantified by a polarimetry station immediately prior to subject administration in a room adjacent to the MR suite (GEHC, Durham, NC). Hyperpolarized ^{3}He MRI coronal static ventilation images were acquired using a ^{3}He coil (14s data acquisition, TR/TE/flip angle = 4.3 ms / 1.4 ms / 7^o, bandwidth = 31.25, FOV = 40 x 40 cm, matrix 128 x 128, 14 slices, 15 mm slice thickness, 0 gap) with multi-slice 2-D simultaneous acquisition of a ventilation image (no T_1-weighted sensitization) and a T_1-weighted image. Only ventilation images with no T_1-weighted sensitization were used in the analysis.

Image Analysis: ^{3}He MRI ventilation segmentation was performed using two-dimensional landmark-based registration of ^{3}He and ^{1}H pulmonary images, and subsequent application of a modified K-means clustering algorithm to the ^{3}He image pixel intensity values within the thoracic cavity. This approach yields ^{3}He images with five different clusters representing unventilated (C1), hypoventilated (C2), ventilated (C3 and C4) and hyperventilated (C5) voxels, ^{3}He ventilation defect cluster (cluster 1) provided ^{3}He ventilation defect volume (VDV), and ^{3}He ventilation cluster volumes (clusters 2-5) were summed to provide ^{3}He ventilation volume (VV). Additionally, the segmented ^{1}H thoracic cavity volume was used to calculate a measurement of ventilation defect as a percent of the lung volume (VDP), as well as a measurement of ventilation as a percent of the lung volume (PVV). For all subjects, semi-automated ^{3}He segmentation was performed for the 10 center slices and repeated 4 times for each subject dataset, for a total of 40 measurements. The repeated measurements were performed by the same observer blinded to subject information and images were randomized in order to reduce any potential measurement or memory bias. All measurements were performed within a 21 day period with at least 48 hours in between successive randomization runs to decrease the potential for bias.

Statistical Analysis: Paired two-tailed t-tests were performed for statistical comparison of scan and rescan pulmonary function and lung volume measurements using SPSS 16.00 (SPSS Inc., Chicago, IL, USA LEAD Technologies, Inc., Chicago, IL). A two-way repeated measures ANOVA was used to determine the interactions between repeated measurements and scan and rescan for all ^{3}He MRI measurements using SPSS 16.00. Linear regression (r^2) and Pearson correlation coefficients (r) were also used to determine the relationships between pulmonary function and ^{3}He MRI measurements using GraphPad Prism version 4.00 (GraphPad Software Inc, San Diego, CA, USA). In all statistical analyses, results were considered significant when the probability of making a Type I error was less than 5% ($p < .05$).

Results: For all 12 CF subjects, there was no significant difference between scan and rescan for pulmonary function measurements as shown in Table 1. Figure 1 shows a representative CF subject at scan and rescan. A two-way repeated measures ANOVA indicated that there was no significant differences for ^{3}He VDP between the repeated measurements (p=.60), however there was a significant difference between VDP at scan and rescan (p<.0001). Moreover, a minimal detectable difference for VDP was 1.5%. There was no correlation between the scan and rescan changes in VDP and the changes in FEV_1 (r=-.17, p=.62), FVC (r=-.33, p=.30), and FEV_1/FVC (r=-.07, p=.82).

Conclusions: Due to the high reproducibility of our semi-automated ^{3}He ventilation segmentation tool, ^{3}He MRI detected statistically significant changes in VDP over 7 ± 2 days, however no significant differences were detected for pulmonary function measurements. Additionally, the detected difference for VDP was twice as large as the minimal detectable difference, indicating that the change in VDP was not likely due to measurement variability and therefore reflects the short term changes in lung ventilation inherent to the physiological day to day changes in CF lung disease. These findings indicate that hyperpolarized ^{3}He MRI measurements may be used as possible clinical intermediate endpoints in adult CF patients to effectively determine treatment response and CF disease progression over time.

Table 1. Scan and rescan hyperpolarized ^{3}He MRI and spirometry measurements

	Scan (n=12)	Rescan (n=12)	Significance of Difference (p)
$FEV_1\ \%_{pred}$ (± SD)	73 (13)	71(13)	0.17*
FVC $\%_{pred}$ (± SD)	87 (12)	86 (10)	0.22*
FEV_1/FVC $\%_{pred}$ (± SD)	74 (11)	73 (12)	0.21*
VDP % (± SD)	22 (11)	19 (13)	<0.0001**

*Significance difference (p<.05) determined using paired two tailed t-test
**Significance difference (p<.05) determined using a two-way repeated measures ANOVA

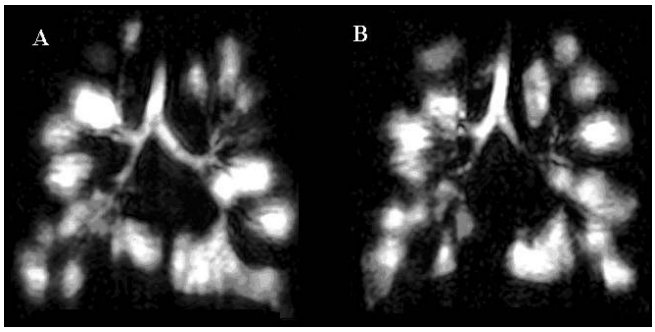

Figure 1. Representative CF subject at scan (A) and rescan (B)