# EVALUATING BRONCHODILATOR EFFECTS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE USING HYPERPOLARIZED HELIUM-3 MAGNETIC RESONANCE IMAGING

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**Purpose:** Chronic obstructive pulmonary disease (COPD) patients often show modest improvements following bronchodilator therapy as measured by $FEV_1$ although indicate reductions in dyspnea and improvements in exercise tolerance. The objective of this study was to evaluate short-acting bronchodilator effects in subjects with chronic obstructive pulmonary disease (COPD) using hyperpolarized helium-3 ($^3$He) magnetic resonance imaging (MRI), plethysmography and spirometry.

**Materials and Methods**

***Subjects:*** Fourteen subjects with COPD provided written informed consent and underwent spirometry, plethysmography and MRI before and 25±2 minutes after administration of 400 μg salbutamol. Significant bronchodilator response was defined according to ATS/ERS guidelines as a change in $FEV_1$ and/or FVC >12% and 0.200L.

***Image Acquisition:*** MRI was performed immediately after pulmonary function tests as well as 25 minutes (±2 minutes) post-bronchodilator, 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°, 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°, 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. For diffusion-weighted imaging, images were obtained using a fast gradient-echo method (FGRE) with centric k-space sampling. 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, 7 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:*** $^3$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. The resultant $^3He/^1H$ segmented images provided five cluster areas that were multiplied by the slice thickness to obtain $^3$He cluster volumes for each slice. The $^1$H thoracic cavity segmentation was also used to calculate the percentage of each cluster volume of 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 ADC was calculated from MRI diffusion-weighted imaging, and ADC maps were generated for the five center slices, using in-house software, for calculation of ADC in the whole lung (WL) and the regions of pre/post overlap (RO) using two-dimensional single point landmark-based registration. Following registration, subsets of pre/post image overlap were identified and mean ADC was calculated in the RO.

***Statistical Analysis:*** Multivariate analysis of variance (MANOVA) followed by repeated measures analysis of variance (ANOVA) was performed for statistical comparison of pre- and post-salbutamol pulmonary function measurements, and a two-way mixed design repeated measures ANOVA was used to determine the interactions between subjects and treatment and bronchodilator response group and treatment for all $^3$He MRI measurements using SPSS 16.00.

**Results:** For all subjects, mean $FEV_1$ significantly increased 120 ± 11mL post-salbutamol (p=.002), and five subjects showed a significant salbutamol response according to ATS/ERS guidelines. All $^3$He cluster volumes were significantly different post-salbutamol, however there were no significant differences detected for either WL ADC or RO ADC, as shown in Table 1. There was however a significant treatment by subject interaction detected for all $^3$He cluster volumes; C1 (p<.0001), C2 (p=.005), C3 ( p<.0001), C4 (p=.04), and C5 (p=.004), as well as for both WL ADC (p=.004) and RO ADC (p<.0001). Figure 1 shows pre- and post-salbutamol ventilation cluster maps for a subject demonstrating large improvements in ventilation distribution. The relationship between $^3$He measurements and bronchodilator responder category (responder or non-responder) were evaluated, and we found that there was a significant difference between C1 (p=.03), C4 (p=.05) and WL ADC (p=.04) for the bronchodilator responder categories at both time points. However, there was no significant difference between the changes in all $^3$He clusters (p<.05) or RO ADC (p=0.16) after salbutamol administration and bronchodilator responder category, but a significant treatment by response group interaction was detected for WL ADC (p=.04).

**Conclusions:** Hyperpolarized $^3$He MRI detected significant reductions in $^3$He clusters that contained no or very diminished MR signal and significant improvements in $^3$He ventilation clusters, but no changes in $^3$He ADC post-salbutamol. Additionally, there were significant interactions detected for salbutamol treatment and all subjects with respect to $^3$He measurements but not for bronchodilator responder subgroups, indicating that bronchodilator responder classification does not provide insight into the regional distribution of ventilation and post-bronchodilator improvements in ventilation distribution occurs in COPD subjects regardless of responder group.

**Table 1.** Pre- and post-salbutamol hyperpolarized $^3$He MRI measurements

| Parameter | Pre-Salbutamol (n=14) | Post-Salbutamol (n=14) | Significance of Difference (ANOVA)* |
|---|---|---|---|
| Cluster 1 % (±SD) | 28 (15) | 23 (14) | <0.0001 |
| Cluster 2 % (±SD) | 16 (5) | 15 (5) | 0.01 |
| Cluster 3 % (±SD) | 30 (12) | 31 (11) | 0.03 |
| Cluster 4 % (±SD) | 19 (8) | 22 (8) | <0.0001 |
| Cluster 5 % (±SD) | 8 (6) | 9 (6) | 0.02 |
| WL ADC (cm$^2$/s) (±SD) | 0.51 (0.07)$^+$ | 0.51 (0.07)$^+$ | 0.56 |
| RO ADC (cm$^2$/s) (±SD) | 0.51 (0.07)$^+$ | 0.51 (0.07)$^+$ | 0.57 |

*Significant difference (p<.05) determined using a two-way repeated measures ANOVA, $^+$n=10

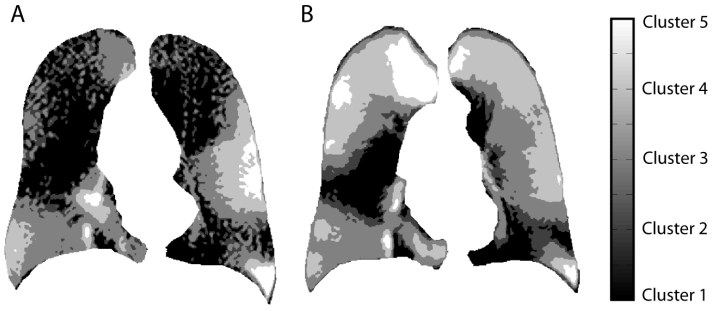


**Figure 1.** $^3$He clusters generated using semi-automated segmentation for a COPD subject at two time points point (A) and (B).