^{3}He MRI and CT Parametric Response Mapping of Small Airways Disease: The Battle-Ground for Ground Truth

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Target Audience: Scientists interested in pulmonary functional MRI and CT thoracic measurements.

Purpose: Hyperpolarized noble gas MRI provides a way to map both functional and structural pulmonary information. ^{3}He MRI gas distribution abnormalities or ventilation defects have been recently shown to reflect both airway remodeling and emphysema in advanced COPD, but in mild COPD these measurements reflect small airways disease.[1] Parametric response mapping (PRM) has recently emerged as a way to use inspiration and expiration CT to regionally identify gas trapping due to small airways disease.[2] Thus, the objective of this work was to directly compare ^{3}He MRI and CT-PRM measurements in patients with COPD and both emphysema and airways disease. We made the assumption that in early or mild COPD, ^{3}He MRI ventilation defects reflected small airways disease and hypothesized that ^{3}He ventilation defect percent (VDP) would be correlated with PRM-measurements of small airways disease.

Methods: All ex-smokers with COPD provided written informed consent to an approved study protocol and were evaluated using hyperpolarized ^{3}He MRI, pulmonary function tests, and inspiratory/expiratory thoracic CT. Hyperpolarized ^{3}He MRI static ventilation images (total acquisition time = 10s; TR/TE/flip-angle = 3.8ms/1.0ms/7°; FOV = 40×40cm; matrix = 128×80; BW = 62.50 kHz; NEX = 1; number of slices = 14; slice thickness = 15mm) and diffusion-weighted images (total data acquisition time = 14s; TR/TE/flip-angle = 6.8ms/4.5ms/8°; FOV = 40×40cm; matrix = 128×128; BW = 62.50 kHz; NEX = 1; number of slices = 7; slice thickness = 30mm) were acquired on a 3T Discovery MR750 (General Electric Health Care, Milwaukee, Wisconsin, USA) system as previously described.[3] ^{3}He MRI ADC and VDP were calculated as previously described.[4] For PRM, non-rigid image registration was performed using NiftyReg[5,6] and using inspiratory and expiratory thoracic CT for voxel-wise comparisons between registered inspiration and expiration CT. Voxels were classified into four categories as previously described.[2] Voxels were classified into four categories based on expiration and inspiration thresholds as follows: (I) inspiration greater than -950 Hounsfield Units (HU) and expiration greater than -856 HU (healthy tissue), (II) inspiration greater than -950 HU and expiration less than -856 HU (small airways disease), (III) inspiration less than -950 HU and expiration less than -856 HU (emphysema), and (IV) inspiration less than -950 HU and expiration greater than -856 HU as shown in Figure 1. Pearson correlation coefficients (r) were used to determine the relationship for ^{3}He MR measurements with PRM categories. Statistical analysis was performed using GraphPad Prism version 6.04 (GraphPad Software Inc, San Diego, California, USA). Results were considered significant when the probability of two-tailed type I error was less than 5% (p<.05).

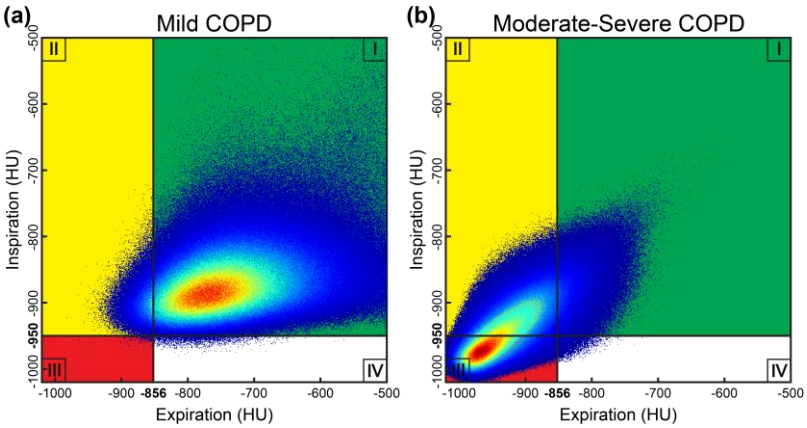

Figure 1. Distributions generated from voxel-wise between registered inspiratory and expiratory CT for A) mild COPD and B) severe COPD. Two thresholds were used to categorize voxels into four quadrants (-856 HU for expiratory CT [gas trapping] and -950 HU for inspiratory CT [emphysema]). In mild COPD, the majority of the voxels were classified as category I (normal tissue) and category II (small airways disease), while for severe COPD the majority of voxels were classified as category III (emphysema).

Table 1. Relationship of ^{3}He MRI with CT-PRM and other COPD measurements.

Parameter	All (n=40) Mean (±SD)	All (n=40) VDP (r)	All (n=40) ADC (r)	Mild COPD (n=26) Mean (±SD)	Mild COPD (n=26) VDP (r)	Mild COPD (n=26) ADC (r)	Moderate-Severe COPD (n=14) Mean (±SD)	Moderate-Severe COPD (n=14) VDP (r)	Moderate-Severe COPD (n=14) ADC (r)
Pack-years (yrs)	35 (26)	.36 *	.47 **	27 (15)	.13	.19	50 (33)	-.73 **	.45
FEV_1 ($\%_{pred}$)	86 (28)	-.73 ***	-.58 ***	102 (17)	.04	.02	56 (16)	-.82 ***	-.53
FEV_1/FVC ($\%_{pred}$)	66 (15)	-.75 ***	-.66 ***	75 (9)	-.17	-.27	50 (10)	.08	-.49
Category II (%)	23 (14)	.52 ***	.54 ***	20 (14)	**.42 ***	.46 *	30 (12)	.49	.40
Category III (%)	4 (8)	.60 ***	.68 ***	2 (2)	.29	.53 **	10 (12)	.45	**.73 ****

FEV_1 = forced expiratory volume in one second; FVC =forced vital capacity; VDP = ventilation defect percent; ADC = apparent diffusion coefficient; $\%_{pred}$ = percent predicted; SD = standard deviation; * = p<.05; ** = p<.01; *** = p<.001.

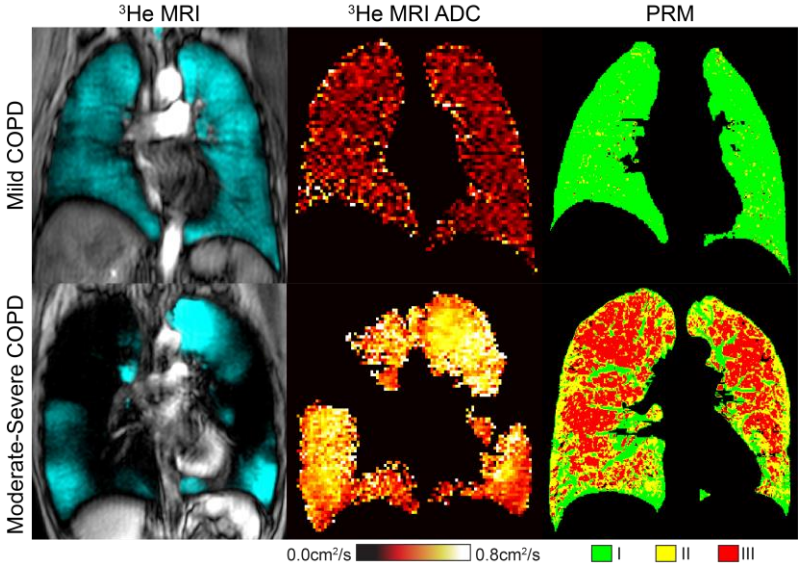

Figure 2. ^{3}He MRI sventilation and ADC maps, CT-PRM maps for a single subject with mild COPD and another with severe COPD. Mild COPD was reflected by fewer ventilation defects, low ADC, and negligible category II (small airways disease) and no category III (emphysema). Severe COPD was reflected by a greater number and volume of ventilation defects, greater ADC, and substantial category III (emphysema). ^{3}He MRI VDP and ADC was significantly correlated with category II CT voxels in mild but not in moderate-severe COPD subjects. ^{3}He MRI ADC, reflecting emphysema, was significantly correlated with category III in mild and moderate-severe COPD subjects.

Results: Figure 1 shows voxel distributions and categories for two subjects with COPD classified based on the GOLD criteria.[7] Table 1 shows the demographic data and Pearson correlation coefficients for ^{3}He MRI measurements with spirometry and PRM categories II (small-airways disease) and III (emphysema). For all subjects (n=40), VDP and ADC were significantly correlated with pack-years, FEV_1 $\%_{pred}$, FEV_1/FVC, category II and III CT voxels. VDP was significantly correlated with category II for mild COPD (r=.42, p<.05), while ADC was significantly correlated with category III in moderate-severe COPD (r=.73, p<.01).

Discussion and Conclusions: In this proof-of-concept demonstration, we generated CT-derived measurements related to gas trapping for comparison to ^{3}He MRI ventilation defects in the same subjects with COPD. We showed that ^{3}He MRI VDP measurements correlated with PRM measurements of small airways disease in mild but not severe grade COPD in whom PRM measurements correlated with emphysematous bullae that were not well-ventilated. This demonstration supports the use of CT-derived PRM measurements in mild COPD where these voxels appear to reflect gas trapping related to small airway remodeling.

References: 1) Kirby, M. *et al. Radiology* (2014); 2) Galban, C. J. *et al. Nature Medicine* (2012); 3) Parraga, G. *et al. Investigative Radiology* (2007); 4) Kirby, M. *et al. Academic Radiology* (2012); 5) Modat, M. *et al. Medical Image Analysis for the Clinic-A Grand Challenge* (2010); 6) Murphy, K. *et al. IEEE Transactions on Medical Imaging* (2011); 7) Vestbo, J. *et al. American Journal of Respiratory and Critical care Medicine* (2013).