

Pulmonary Functional MRI to Phenotype COPD and Evaluate Treatment Efficacy: Intermediate Endpoints and Predictors of Efficacy when Conventional endpoints fail?

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Target Audience: Scientists and clinicians interested in pulmonary functional magnetic resonance imaging (MRI) to phenotype and evaluate therapy in respiratory disease.

Purpose: In all mammals, the respiratory system is relatively over-engineered for most every-day tasks and it is not until respiratory disease is well-advanced that symptoms are recognized and conventional clinical measurements such as the forced expiratory volume in 1 s (FEV₁) detect abnormalities. In part because diagnosis is typically made when disease is advanced, for patients with chronic obstructive lung disease, (COPD), non-invasive imaging measurements including those provided by computed tomography (CT) and MRI are not used for clinical diagnosis or for monitoring disease progression. Moreover, symptoms and FEV₁ measurements and not imaging biomarkers or phenotypes are used to guide therapy and patient management decisions. Unfortunately however, airflow and lung volume measurements cannot provide a way to quantify changes in parenchymal tissue abnormalities (emphysema) or airways abnormalities including airway morphologies, and mucous plugging (chronic bronchitis). We think that non-invasive imaging measurements of the direct anatomical and functional contributions to symptoms and airflow limitation can be used as intermediate endpoints in clinical trials of new therapies. Therefore, the objective of this proof-of-concept study was to evaluate hyperpolarized ³He MRI measurements of emphysema and airways disease in a study of the 4-week treatment efficacy of a handheld airway clearance device for mobilizing mucous secretions and clearing airways in COPD patients with well-advanced disease. We hypothesized that there would be ³He MRI improvements following airway clearance therapy in COPD and that MRI measurements of underlying phenotypes would provide a way to stratify patients based on airways disease/emphysema and based on imaging response.

Methods: Subjects with a diagnosis of COPD provided written informed consent to an 8-week randomized controlled cross-over study protocol approved by the local research ethics board and Health Canada evaluating the efficacy of an Oscillatory Positive Expiratory Pressure (oPEP) therapy system. All subjects underwent spirometry, plethysmography, six-minute walk test (6MWT), the St. George's Respiratory (SGRQ) and Patient Evaluation Questionnaires (PEQ) at each of 5 visits and hyperpolarized ³He MRI at baseline, week 4 and week 8. 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 Subjects were instructed to inhale a gas mixture from a 1.0L Tedlar bag (Jensen Inert Products, NJ, USA) from functional residual capacity and image acquisition was performed in 8-15s under breath-hold conditions. Conventional ¹H MRI was performed prior to hyperpolarized ³He MRI as previously described.¹ For hyperpolarized ³He MRI, a polarizer system (HeliSpin, General Electric Health Care, Durham, NC, USA) was used to polarize ³He gas to 30-40% and doses (5mL/kg body weight) were administered in 1.0L Tedlar bags diluted with N₂. For ³He static ventilation imaging, images were obtained using a fast gradient-recalled echo (FGRE) sequence (14 s breath hold; repetition time (TR) = 4.3 ms; echo time (TE) = 1.4 ms; flip angle = 7 degrees; field of view = 40 x 40 cm; matrix, 128 x 128; 14-17 slices; slice thickness = 15 mm; 0 mm gap). For ³He MRI diffusion-weighted imaging, images were obtained using an FGRE method. 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/cm²), were acquired. As previously described,² ³He MRI static ventilation semi-automated segmentation was performed to generate the ventilation defect percent (VDP). We also generated apparent diffusion coefficient (ADC) measurements of underlying parenchymal abnormalities (emphysema). A multivariate repeated measures analysis of variance (ANOVA) was used to determine the difference between ³He MRI measurements, pulmonary function measurements and symptoms on and off therapy using IBM SPSS Statistics 21.0 (SPSS Inc., Chicago, IL, USA). The smallest detectable difference (SDD), defined as the smallest difference that can be measured with prospectively determined confidence not due to measurement variability was calculated using baseline repeated ³He VDP measurements.²

Results: Fourteen non-phenotyped COPD subjects with well-advanced disease (6 males, mean age=73±5yrs) completed the study. For all subjects, there was improved dyspnea and ease in bringing up sputum on oPEP therapy. The SDD for ³He MRI VDP was determined based on the reproducibility of repeated measurements and was 2%. Six subjects (3 males, mean age 73±5yrs) were classified as having an improvement in VDP that was greater than the SDD on oPEP therapy (Imaging Improvement Group: off VDP=20±11, on VDP=18±11, p=0.04) and eight subjects (3 males, mean age 72±7yrs) were classified as not having an improvement in VDP while on oPEP therapy (No Imaging Improvement Group: off VDP=19±11, on VDP=23±10, p=0.02). Figure 1 shows a representative subject from the imaging improvement group and no imaging improvement group, the improvement in ³He gas distribution while on oPEP is apparent (white arrows) in the subject classified as having imaging improvement. As shown in Table 1, the imaging improvement group also had improved FVC%_{pred}, 6MWD and symptoms; improvements in pulmonary function and symptoms were not observed in the no imaging improvement group. Compared with the no imaging improvement group, subjects with an imaging improvement had a significantly different smoking history (p=0.02) and there was a trend towards lower ³He MRI ADC (p=0.17) and lower CT RA950 (p=0.26).

Discussion: Following therapy, 6/14 subjects were classified as having improved ³He gas distribution, and in this sub-group improvements in standard measurements of pulmonary function and exercise capacity were also observed. Retrospective analysis of those subjects with imaging improvement suggests that airway clearance therapy may be more effective in COPD subjects with less smoking history and parenchymal tissue abnormalities (emphysema).

Conclusions: In a small group of COPD subjects, improvements in objective measurements of pulmonary function and exercise capacity following airway clearance therapy were only observed in a sub-group of subjects with imaging improvement.

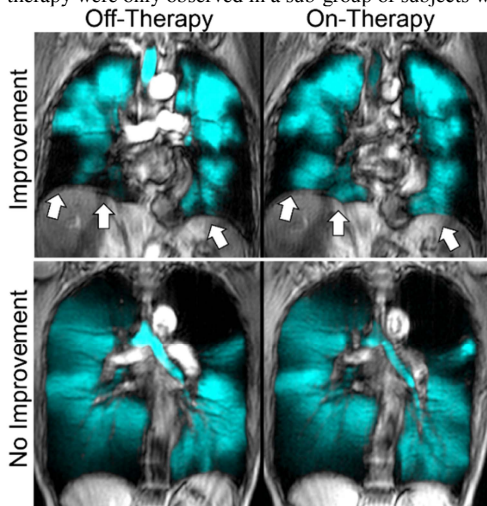


Figure 1. Hyperpolarized ³He MRI (in blue) registered to the corresponding thoracic ¹H MRI for representative subjects with and without imaging improvement. Improved ³He gas distribution on oPEP therapy is apparent (white arrows) for the representative imaging improvement subject.

References: 1. Kirby M *et al. Acad Rad.* (2012); 2. Eliasziw M. *et al. Phys Ther.* (1994).

Table 1. Pulmonary function tests, 6MWD, SGRQ, PEQ, and hyperpolarized ³He MRI measurements on and off oPEP therapy for the imaging improvement and no imaging improvement group.

	Imaging Improvement (n=6)			No Imaging Improvement (n=8)		
	Off	On	sd' (p)	Off	On	sd' (p)
Pulmonary Function Tests (±SD)						
FEV ₁ % _{pred}	58 (12)	58 (13)	0.91	63 (15)	61 (16)	0.17
FVC % _{pred}	84 (13)	86 (12)	0.04	99 (7)	99 (5)	0.93
FEV ₁ /FVC %	52 (6)	50 (8)	0.27	47 (12)	46 (12)	0.10
RV % _{pred}	154 (32)	149 (17)	0.62	138 (26)	144 (29)	0.44
TLC % _{pred}	111 (9)	108 (8)	0.48	114 (9)	115 (10)	0.78
DL _{CO} % _{pred}	61 (18)	60 (19)	0.70	50 (25)	47 (21)	0.50
6MWD m (±SD)	394 (100)	399 (99)	0.009	375 (102)	370 (107)	0.47
Patient Evaluation Questionnaire (±SD)						
Cough	Moderate	Mild	-	Mild	Mild	-
Dyspnea	Moderate	Mild	-	Mild	Mild	-
Ease Bring up	No Ch	Slight	-	No Ch	No Ch	-
Sputum		Impvmt				
Global Evaluation	No Ch	Slight	-	No Ch	No Ch	-
		Impvmt				
³He MRI (±SD)						
VDP %	20 (11)	18 (11)	0.04	19 (11)	23 (10)	0.02
ADC cm ² /s	0.39 (0.08)	0.39 (0.08)	0.58	0.47(0.10)	0.47(0.12)	0.33

SD=Standard Deviation; FEV₁=Forced Expiratory Volume in 1s; %_{pred}=Percent Predicted; FVC=Forced Vital Capacity; RV=Reserve Volume; TLC=Total Lung Capacity; 6MWD=6-minute walk distance; VDP=Ventilation Defect Percent; ADC=Apparent Diffusion Coefficient; No Ch=No Change; Slight Impvmt=Slight Improvement; sd=significance of difference. *(p<.05) determined using repeated measures ANOVA.