Automated Registration-Segmentation Pipeline to Generate Lobar Ventilation Measurements in Diffuse and Localized Bronchiectasis

Sarah Svenningsen[1,2], Fumin Guo[1,3], Roya Etemad-Rezai[4], David G McCormack[5], and Grace Parraga[1,2]

[1]*Imaging Research Laboratories, Robarts Research Institute, London, Ontario, Canada,* [2]*Department of Medical Biophysics, The University of Western Ontario, London, Ontario, Canada,* [3]*Graduate Program in Biomedical Engineering, The University of Western Ontario, London, Ontario, Canada,* [4]*Department of Medical Imaging, The University of Western Ontario, London, Ontario, Canada,* [5]*Division of Respirology, Department of Medicine, The University of Western Ontario, London, Ontario, Canada*

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

Purpose: Current treatment methods and clinical endpoints of respiratory disease target and evaluate global lung measurements, providing no regional information. In contrast to global lung measurements made at the mouth, regional measurements of lung function may provide increased sensitivity to disease progression or treatment response. Regional measurements of lung function can be estimated using non-invasive MRI methods and such measurements have been proposed for use as intermediate endpoints in clinical trials of new therapies. We think that regional disease measurements, provided by MRI, are most important for those patients whose respiratory disease does not affect the whole lung because changes may be masked by contributions from healthy lung regions. For example, airways disease involvement in bronchiectasis is frequently focal or multifocal. Therefore, the objective of this proof-of-concept study was to regionally quantify and evaluate hyperpolarized ^{3}He MRI ventilation measurements, using an automated registration-segmentation pipeline, in a small group of patients with bronchiectasis. We hypothesized that regional ventilation measurements would enable a direct comparison of bronchiectatic lung lobes with more normal tissue in the same patient, providing a new way to regionally evaluate response to therapy.

Methods: Participants with bronchiectasis (45-85 years) provided written informed consent and were evaluated using spirometry, plethysmography, six-minute walk test (6MWT), the St. George's Respiratory questionnaire (SGRQ), hyperpolarized ^{3}He MRI and CT. Imaging was performed on a whole body 3.0 Tesla Discovery MR750 system (General Electric Health Care, WI, USA). 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 ^{1}H MRI was performed prior to hyperpolarized ^{3}He MRI as previously described.[1] For hyperpolarized ^{3}He MRI, a turn-key polarizer system (HeliSpin™, Polarian Inc., NC, USA) was used to polarize ^{3}He gas to 30-40% and doses (5mL/kg body weight) diluted with N_2 were administered. For ^{3}He static ventilation imaging, images were obtained using a fast gradient-recalled echo 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 80; 14-17 slices; slice thickness = 15 mm; 0 mm gap). CT was performed on a 64-slice Lightspeed VCT scanner (General Electric Health Care, WI, USA). A single spiral acquisition of the entire lung was acquired from apex to base with subjects in breath-hold after inhalation of N_2 (detector configuration of 64×0.625 mm, 120 kVp, 100 effective mA, tube rotation time of 500 ms and a pitch of 1.0). Reconstruction of the data was performed using a standard convolution kernel and a slice thickness of 1.25 mm.

Regions of signal void were quantified as the ^{3}He ventilation defect percent for the whole lung (WL VDP) and each lobe (RUL VDP, RML VDP, RLL VDP, LUL VDP, and LLL VDP) using a semi-automated segmentation and automated registration pipeline. Briefly, thoracic CT images were analyzed using Pulmonary Workstation 2.0 (VIDA Diagnosis Inc., IA, USA) to segment the whole lung cavity and individual lobes to generate the CT-derived whole lung cavity volume (WL V) and lobe-specific volumes (RUL V, RML V, RLL V, LUL V, and LLL V). ^{1}H and ^{3}He images were resampled to isotropic space (1.56mm x 1.56mm x 1.56mm) for subsequent registration procedures. CT-^{1}H MRI registration was performed using an affine[1] followed by a deformable method[2] and ^{3}He-^{1}H MRI registration was performed using a rigid method.[1] The CT-^{1}H MRI deformation field was used to deform the CT-derived masks to the ^{1}H-^{3}He MRI space. Adapted from previously described methods, ^{3}He images were segmented using a 3D hierarchical k-means clustering method,[3] where the first cluster represents signal void or ventilation defect volume (VDV). Whole lung VDP was calculated by normalizing the whole lung VDV (WL VDV) to the CT-derived WL V. Similarly, VDP was calculated for each lobe by normalizing the lobe specific VDV to the respective CT-derived lobe-specific volumes. Qualitative CT evaluation was performed by an expert chest radiologist to determine which lung lobes contained bronchiectasis (bronchiectatic and not-bronchiectatic), and the distribution of bronchiectasis was categorized as diffuse (bronchiectasis in each lobe) or localized (bronchiectasis in <5 lobes).

One-way analysis of variance (ANOVA) and Tukey's multiple comparison tests were used to evaluate differences in lobar VDP. Additionally, a two-tailed paired t-test was used to evaluate the difference between VDP in the bronchiectatic and not-bronchiectatic lobes. All statistics were performed using GraphPad Prism version 6.02 (GraphPad, Inc., San Diego) and results were considered statistically significant when the probability of making a Type I error was less than 5% ($p < 0.05$).

Results: Patient characteristics and imaging measurements are provided in Table 1 for 15 patients with bronchiectasis. For three patients, there was CT evidence of bronchiectasis in each and every lung lobe (diffuse bronchiectasis) and for 12 patients bronchiectasis was localized to < 5 lobes (localized bronchiectasis). Figure 1 shows hyperpolarized ^{3}He MRI ventilation images for a representative patient with diffuse bronchiectasis and another with localized bronchiectasis. For the participant with diffuse disease, whole lung and lobar VDP were similar except for the left lower lobe (LLL). For the volunteer with localized bronchiectasis, VDP was greatest in the right middle lobe (RML) and very low in the right and left upper lobe and right lower lobe. As shown in Figure 2A that shows data for all patients, right middle and right lower lobe VDP was significantly greater than LUL ($p=0.004$, $p=0.02$). Figure 2B shows that for patients with localized bronchiectasis, VDP in the structurally abnormal lobes was significantly greater than in structurally normal lobes (normal: 9±7%, abnormal: 21±16%, $p=0.03$).

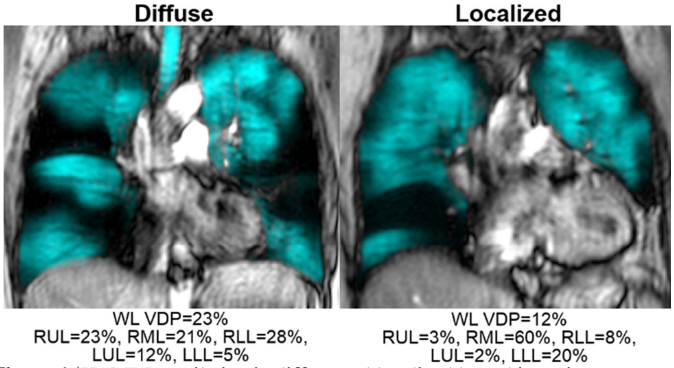

Figure 1. ^{3}He MRI ventilation in diffuse and localized bronchiectasis.

Discussion: Ventilation MRI identified functional abnormalities in patients with either diffuse or localized bronchiectasis. Regional measurements of ventilation were significantly worse in lung lobes with CT evidence of bronchiectatic abnormalities. These regional measurements are novel intermediate endpoints that can be used in clinical trials of new therapies.

Conclusions: Lobe-specific MRI ventilation measurements provide a way to probe lung function in those regions that are structurally abnormal on the basis of CT evidence (bronchiectatic airways). Quantitative regional measurements of pulmonary ventilation are more sensitive to therapy response than currently used global measurements of airflow and lung volume, made at the mouth.

Table 1. Subject measurements

Parameter (±SD)	**Bronchiectasis** (n=15)
Age yrs	69 (10)
Male Sex	4
BMI kg/m^2	24 (4)
$FEV_1\%_{pred}$	69 (21)
$FVC\%_{pred}$	73 (21)
6MWD (m)	411 (87)
SGRQ	66 (20)
WL VDP%	17 (7)
RUL VDP%	11 (10)
RML VDP%	28 (22)
RLL VDP%	20 (16)
LUL VDP%	8 (7)
LLL VDP%	20 (17)

SD=Standard Deviation, BMI=Body Mass Index, FEV_1=forced expiratory volume 1 second; FVC=forced vital capacity; WL=whole lung; VDP=ventilation defect percent; RUL=right upper lobe; RML=right middle lobe; RLL=right lower lobe; LUL=left upper lobe; LLL=left lower lobe.

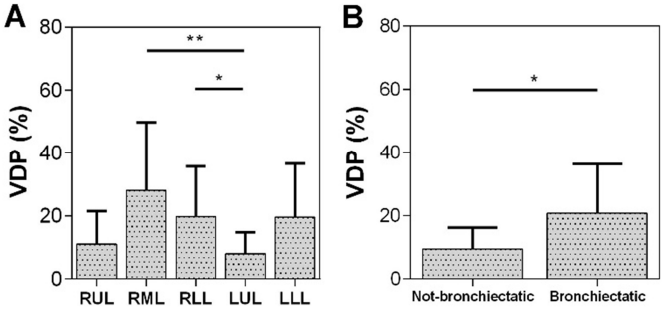

Figure 2. **A)** Lobar ^{3}He MRI VDP for all bronchiectasis patients. B) Lobar VDP for bronchiectatic and non-bronchiectatic lobes for 12 patients with localized bronchiectasis. Error bars=standard deviation. *p<0.05, **p<0.01.

References:

1. Ourselin S et al. MICCAI. 2002:140-147.
2. Modat Met al. Comp Meth Prog Bio. 2010;98(3):278-284.
3. Kirby M et al. Acad Radiol. 2012;19(2):141-152.