Original Investigations

Ventilation Heterogeneity in Ex-smokers without Airflow Limitation

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Rationale and Objectives: Hyperpolarized ^{3}He magnetic resonance imaging (MRI) ventilation abnormalities are visible in ex-smokers without airflow limitation, but the clinical relevance of this is not well-understood. Our objective was to phenotype healthy ex-smokers with normal and abnormally elevated ventilation defect percent (VDP).

Materials and Methods: Sixty ex-smokers without airflow limitation provided written informed consent to ^{3}He MRI, computed tomography (CT), and pulmonary function tests in a single visit. ^{3}He MRI VDP and apparent diffusion coefficients (ADCs) were measured for whole-lung and each lung lobe as were CT measurements of emphysema (relative area [RA] with attenuation ≤ -950 HU, RA_{950}) and airway morphology (wall area percent [WA%], lumen area [LA] and LA normalized to body surface area [LA/BSA]).

Results: In 42 ex-smokers, there was abnormally elevated VDP and no significant differences for pulmonary function, RA_{950}, or airway measurements compared to 18 ex-smokers with normal VDP. Ex-smokers with abnormally elevated VDP reported significantly greater ^{3}He ADC in the apical lung (right upper lobe [RUL], $P = .02$; right middle lobe [RML], $P = .04$; and left upper lobe [LUL], $P = .009$). Whole lung ($r = 0.40$, $P = .001$) and lobar VDP (RUL, $r = 0.32$, $P = .01$; RML, $r = 0.46$, $P = .002$; right lower lobe [RLL], $r = 0.38$, $P = .003$; LUL, $r = 0.35$, $P = .006$; and left lower lobe, $r = 0.37$, $P = .004$) correlated with regional ^{3}He ADC. Although whole-lung VDP and CT airway morphology measurements were not correlated, regional VDP was correlated with RUL LA ($r = -0.37$, $P = .004$), LA/BSA ($r = -0.42$, $P = .0008$), RLL WA % ($r = 0.28$, $P = .03$), LA ($r = -0.28$, $P = .03$), and LA/BSA ($r = -0.37$, $P = .004$).

Conclusions: Abnormally elevated VDP in ex-smokers without airflow limitation was coincident with very mild emphysema detected using MRI and regional airway remodeling detected using CT representing a subclinical obstructive lung disease phenotype.

Key Words: Hyperpolarized ^{3}He magnetic resonance imaging; computed tomography; airways disease; emphysema.

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow limitation caused by small airway remodeling, airway obliteration (1), and emphysematous tissue destruction (2). COPD is typically diagnosed after respiratory symptoms become obvious and intolerable (3), and this usually occurs when spirometry measurements of lung function reflect airflow limitation and obstruction. However, it is well understood that ex- and current-smokers may report normal lung function (3) and mild symptoms, and this may represent an early or "subclinical" phase. A deep understanding of the underlying morphologic changes that accompany this "subclinical" phase is lacking, mainly because methods for evaluating pulmonary function cannot detect very mild or early structure–function abnormalities.

Hyperpolarized ^{3}He magnetic resonance imaging (MRI) ventilation heterogeneity has been shown in patients with pulmonary diseases such as COPD (4,5), asthma (6,7), and cystic fibrosis (8). At the same time, however, preclinical or subclinical ^{3}He ventilation heterogeneity has also been observed in volunteers without clinical signs or symptoms of lung disease such as healthy elderly never-smokers (9), ex-smokers without airflow limitation (10), in second-hand smoke exposed adults (11), and current-smokers without disease (12). To evaluate the underlying anatomic and structural determinants of ventilation heterogeneity, thoracic x-ray computed tomography (CT) has been used to help determine the spatial relationship of airways disease and emphysema with ventilation

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abnormalities. For example, recent work (13) provided evidence that in COPD, ^{3}He ventilation defects represent regions of emphysema and airways disease and that this relationship depends on disease severity. In asthma (7), ^{3}He ventilation heterogeneity was also shown to be spatially related to abnormally remodeled airways. However, the pathophysiological origins and contributions of very mild or subclinical airways disease and emphysema to ventilation heterogeneity in ex-smokers without airflow limitation have not been investigated and remain poorly understood.

To better understand the pathophysiological features of ventilation heterogeneity in the "subclinical phase" of obstructive lung disease in otherwise normal healthy ex-smokers, we evaluated a group of well-characterized ex-smokers without airflow limitation using both MRI and CT. Because of previous research that has suggested that microstructural alveolar remodeling and small airway obliteration occur in subclinical and mild COPD (1,2,11,12), we hypothesized that in normal ex-smokers, ^{3}He ventilation abnormalities would be spatially and quantitatively related to a combination of very mild airways disease and emphysema.

MATERIALS AND METHODS

Study Participants

Study participants provided written informed consent to a protocol approved by a local research ethics board and Health Canada, and the protocol was compliant with the Personal Information Protection and Electronic Documents Act (Canada) and Health Insurance Portability and Accountability Act (USA). Research volunteers were recruited from a tertiary health care practice. Each visit was completed in approximately 2 hours when spirometry, plethysmography, the six-minute walk test, St. George's Respiratory Questionnaire, ^{3}He MRI, and CT were completed.

Spirometry and Plethysmography

Spirometry was performed according to the American Thoracic Society guidelines (14). Whole-body plethysmography was used to measure lung volumes (MedGraphics Corporation, St. Paul, MN), and the attached gas analyzer was used to measure diffusing capacity of the lung for carbon monoxide.

Imaging

MRI was performed on a 3T Discovery MR750 (General Electric Health Care, Milwaukee, WI) system with subjects in inspiratory breath hold at functional residual capacity (FRC) + 1 L. ^{1}H MRI was acquired before ^{3}He MRI after inhalation of 1 L high purity, medical grade nitrogen (N_2) from FRC using the whole-body radiofrequency coil and a fast spoiled gradient-recalled-echo sequence (FGRE; total scan time ~ 12 s, repetition time [TR] = 4.3 ms, echo time [TE] = 1.0 ms, flip angle = 30°, partial echo percent = 62.5%, bandwidth [BW] = 62.5 kHz, field of view [FOV] = 40 × 40 cm, matrix size = 128 × 80 [zero padded to 128 × 128], number of excitations [NEXs] = 1, slice thickness = 15 mm, number of slices ~ 14 [depending on subject size], 0 gap). ^{3}He MRI was acquired using a rigid elliptical transmit–receive chest coil (RAPID, Biomedical, Rimpar, Wuerzburg, Germany) with subjects in inspiratory breath-hold after inhalation from FRC of a 1 L mixture of hyperpolarized ^{3}He (5 mL/kg body weight) diluted with N_2. ^{3}He static-ventilation images were acquired using a partial-echo FGRE sequence (total scan time ~ 10 s, TR = 3.8 ms, TE = 1.0 ms, flip angle = 7°, partial echo percent = 62.5%, BW = 62.5 kHz, FOV = 40 × 40 cm, matrix size = 128 × 80 [zero padded to 128 × 128], NEX = 1, slice thickness = 15 mm, number of slices ~ 14 (depending on subject size), 0 gap). ^{3}He diffusion-weighted MR imaging was completed using a centric k-space sampled FGRE sequence (total scan time ~ 14 s, TR = 6.8 ms, TE = 4.5 ms, flip angle = 8°, partial echo percent = 62.5%, BW = 62.5 kHz, FOV = 40 × 40 cm, matrix size = 128 × 80 [zero padded to 128 × 128], NEX = 1, slice thickness = 30 mm, number of slices ~ 7, 0 gap) that acquired two interleaved slices with and without diffusion sensitization (b = 1.6 s/cm^2, maximum gradient amplitude (G) = 1.94 G/cm, rise/fall time = 0.5 ms, gradient duration = 0.46 ms, and diffusion time = 1.46 ms).

CT was acquired within 30 minutes of MRI using a 64 slice Lightspeed VCT system (General Electric Health Care). Subjects were transported to the CT suite by wheelchair to prevent the potential for exercise-induced changes between MRI and CT image acquisitions. CT was acquired during inspiratory breath-hold of FRC+1 L of N_2 using a single spiral acquisition from apex to base with subjects in the supine position (detector configuration = 64 × 0.625 mm, tube voltage = 120 kVp, tube current = 100 mAs, tube rotation time = 500 ms, and pitch = 1). The total effective dose was 1.8 mSv as calculated using manufacturer settings and the ImPACT CT dosimetry calculator based on Health Protection Agency (UK) NRPB-SR250.

Image Analysis

Ventilation heterogeneity or regions of "signal void" were quantified as ^{3}He ventilation defect percent (VDP) using semiautomated software generated in MATLAB (Mathworks, Natick, MA) as previously described (15). Lobar VDP was generated by registering the segmented thoracic CT lobe mask from VIDA Pulmonary Workstation 2.0 (VIDA Diagnostics Inc., Coralville, IA) to ^{3}He MRI ventilation images using deformable registration, and generating VDP for each lobe (right upper lobe [RUL], right middle lobe [RML], right lower lobe [RLL], left upper lobe [LUL], left lower lobe [LLL]) using hierarchical k-means clustering (15).

All ex-smokers were classified as having normal or abnormally elevated VDP using a threshold based on the upper limit