European Journal of Radiology 79 (2011) 140–146

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Hyperpolarized ^{3}He magnetic resonance imaging: Preliminary evaluation of phenotyping potential in chronic obstructive pulmonary disease

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ARTICLE INFO

Article history:
Received 21 September 2009
Received in revised form 16 October 2009
Accepted 21 October 2009

Keywords:
Helium-3
Magnetic resonance imaging
Phenotype
Chronic obstructive pulmonary disease
Pulmonary ventilation
Emphysema

ABSTRACT

Rationale and objectives: Emphysema and small airway obstruction are the pathological hallmarks of chronic obstructive pulmonary disease (COPD). The aim of this pilot study in a small group of chronic obstructive pulmonary disease (COPD) patients was to quantify hyperpolarized helium-3 (^{3}He) magnetic resonance imaging (MRI) functional and structural measurements and to explore the potential role for ^{3}He MRI in detecting the lung structural and functional COPD phenotypes.
Materials and methods: We evaluated 20 ex-smokers with stage I (n = 1), stage II (n = 9) and stage III COPD (n = 10). All subjects underwent same-day plethysmography, spirometry, ^{1}H MRI and hyperpolarized ^{3}He MRI at 3.0 T. ^{3}He ventilation defect percent (VDP) was generated from ^{3}He static ventilation images and ^{1}H thoracic images and the ^{3}He apparent diffusion coefficient (ADC) was derived from diffusion-weighted MRI.
Results: Based on the relative contribution of normalized ADC and VDP, there was evidence of a predominant ^{3}He MRI measurement in seven patients (n = 3 mainly ventilation defects or VDP dominant (VD), n = 4 mainly increased ADC or ADC dominant (AD)). Analysis of variance (ANOVA) showed significantly lower ADC for subjects with predominantly elevated VDP (p = 0.02 compared to subjects with predominantly elevated ADC; p = 0.008 compared to mixed group) and significantly decreased VDP for subjects with predominantly elevated ADC (p = 0.003, compared to mixed group).
Conclusion: In this small pilot study, a preliminary analysis shows the potential for ^{3}He MRI to categorize or phenotype COPD ex-smokers, providing good evidence of feasibility for larger prospective studies.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is the most common chronic, terminal respiratory disease worldwide and it continues to grow in prevalence [1] and yet has a very poor prognosis, despite aggressive therapy [1–3]. Although widespread pulmonary inflammation [4,5] and diffuse lung tissue alterations are often observed [5], obstruction of the small airways (airways disease) and tissue destruction in the pulmonary parenchyma (emphysema) are the hallmark pathologies [6]. Accordingly, both airways disease and emphysema contribute to the clinical course of COPD, although the underlying mechanisms of both pathologies and the proportional contributions of these and their relationship outcomes are not completely understood.

The current functional definition of COPD [7] relies on the spirometric measurement of airflow obstruction. A fundamental limitation exists however, because the anatomy and physiology

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doi:10.1016/j.ejrad.2009.10.028

of the lung is complex and spirometry measurements reflect the global sum of all the different possible COPD pathologies including small airways disease, emphysema (i.e., parenchymal destruction), chronic bronchitis (i.e., large airway remodeling), and bronchiectasis (i.e., abnormal dilation of bronchi and bronchioles) [6].

The limitation of spirometry for differentiating between these pathologies or phenotypes has severely limited the scope of basic research and clinical studies that evaluate the relationship between these morphological phenotypes, disease pathogenesis, progression, and patient outcomes. Accordingly, one major goal of COPD research is to find a way to identify patients with these different underlying pathological "phenotypes", which has the potential to have a profound effect on patient care and treatment options. In this regard, non-invasive high-resolution multi-detector X-ray computed tomography (CT) [8–11] has been shown to detect unique and quantitative phenotypes of both emphysema and airway disease [12–14] with the potential to determine the contributions of both airway and airspace changes in COPD. Recent results suggest that CT-derived phenotypes provide evidence of underlying phenotype dominance in approximately 40% of subjects [12].

Hyperpolarized ^{3}He magnetic resonance imaging (MRI) has emerged as research method that is complementary to CT because it allows for simultaneous visualization of tissue structure and regional airway function at high spatial and temporal resolution, without the use of ionizing radiation. In particular, the measurement of the ^{3}He apparent diffusion coefficient (ADC) [15], which is a surrogate measurement of airspace size [16–19], has been previously histologically validated [20] and correlated with CT measurements of emphysema [21]. Ventilation defects or signal voids in ^{3}He spin density images are hypothesized to reflect airflow limitation related to airway narrowing or closure [22], but the exact pathology underlying ^{3}He ventilation defects has yet to be determined. Importantly, both ^{3}He MRI ADC and ventilation measurements have been shown to be highly reproducible [23–25], sensitive to age [26–28] and to disease-related changes [25,29–32].

Here we describe the results of a proof-of-principle and hypothesis-generating preliminary study where we explore the potential of hyperpolarized ^{3}He MRI to classify (or phenotype) individual COPD ex-smokers based on the relative contributions of ventilation defect and ADC measurements. To our knowledge, this is the first study aimed at evaluating the potential for ^{3}He MRI to detect phenotypes based on the proportional contributions of COPD structural and functional measurements.

2. Materials and methods

2.1. Subjects

Twenty subjects were enrolled from the general population of the local tertiary health care center as well as directly from the COPD clinics at three local teaching hospitals. All subjects provided written informed consent to the study protocol approved by the local research ethics board and Health Canada and the study was compliant with both the Health Insurance Portability and Accountability Act (HIPAA, USA) and the Personal Information Protection and Electronic Documents Act (PIPEDA, Canada). Subjects were categorized according to Global initiative for Obstructive Lung Disease (GOLD) criteria [33] and required a COPD diagnosis of at least one year, with a smoking history of at least 10-pack-years and additional inclusion and exclusion criteria as previously reported [25].

2.2. Pulmonary function tests

Subjects were screened for MRI and coil compatibility (inner diameter of elliptical coil = 50 cm) and underwent a physical exam, plethysmography and spirometry both of which were performed according to American Thoracic Society guidelines [34]. Briefly, spirometry was performed pre- and post-bronchodilator using an *ndd EasyOne* spirometer (ndd Medizintchnik AG, Zurich, CH) reporting forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) and a minimum of three acceptable spirometry maneuvers were carried out with the best FEV_1 and FVC selected for analysis. Whole body plethysmography (MedGraphics Corporation, 350 Oak Grove Parkway, St. Paul, MN, USA) was also performed within meters of the MR scanner for the measurement of the total lung capacity (TLC), the inspiratory capacity (IC), the residual volume (RV), and the functional residual capacity (FRC).

2.3. Safety monitoring and hyperpolarized ^{3}He administration

Prior to MRI, supine vital signs and arterial O_2 levels measured by pulse oximetry were recorded, and subjects were administered a practice dose of mixed ^{4}He–N_2 gas while seated outside the scanner. Digital pulse oximetry was used to monitor arterial blood oxygen levels during MR scanning and all breath-hold maneuvers. Hyperpolarized ^{3}He gas was provided by a turn-key, spin-exchange polarizer system (HeliSpin^{TM}, GEHC, Durham, NC) as previously described [35]. In a typical study this system provided 30% polarization in 12 h. Doses (5 mL/kg) were delivered in 1 L plastic bags (Tedlar®, Jensen Inert Products, Coral Springs, FL) diluted with ultrahigh purity, medical grade nitrogen (Spectra Gases, Alpha, NJ). The ^{3}He gas dose was administered to subjects after completing a tidal breath exhalation (i.e., FRC) and imaging was performed with the subject in breath-hold from FRC.

2.4. Imaging

Magnetic resonance imaging was performed on a whole body 3.0 T Excite 12.0 MRI system (GEHC, Milwaukee, WI, USA) with broadband imaging capability as previously described [35]. All helium imaging employed a whole body gradient set with maximum gradient amplitude of 1.94 G/cm and a single channel, rigid elliptical transmit/receive chest coil (RAPID Biomedical GmbH, Wuerzburg, Germany). The basis frequency of the coil was 97.3 MHz and maximum excitation power was 3.2 kW using an AMT 3T90 RF power amplifier (GEHC, Wilwaukee, WI, USA).

Two-dimensional multi-slice coronal ^{1}H scans were acquired prior to ^{3}He imaging with subjects scanned during 1 L breath-hold of ^{4}He/N_2 from FRC using the whole body radiofrequency (RF) coil and proton fast spoiled gradient-echo (16 s total data acquisition, repetition time (TR) = 4.7 ms, echo time (TE) = 1.2 ms, flip angle = 30°, bandwidth (BW) = 31.25, field-of-view (FOV) = 40 cm × 40 cm, matrix 128 × 128, 14 slices, 15 mm slice thickness, 0 mm gap). For diffusion-weighted ^{3}He imaging, multi-slice coronal images were obtained using a fast gradient-echo method (FGRE) with centric k-space sampling. Two interleaved images (14 s total data acquisition, TR = 7.6 ms, TE = 3.7 ms, flip angle = 8°, BW = 31.25, FOV = 40 cm × 40 cm, matrix = 128 × 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 = 0.46ms, Δ = 1.46 ms, b = 1.6 s/cm^2), were acquired for each slice. For ventilation images, multi-slice coronal images were also obtained using the same ^{3}He coil (14 s total data acquisition, TR = 4.3 ms, TE = 1.4 ms, flip angle = 7°, BW = 31.25, FOV = 40 cm × 40 cm, matrix 128 × 128, 15 slices, 10 mm slice thickness, 0 mm gap).

2.5. Image analysis

^{3}He ventilation image measurements and ^{3}He diffusion-weighted image analyses were performed in an image visualization