Pulmonary Functional Magnetic Resonance Imaging:

Asthma Temporal–Spatial Maps

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Rationale and Objectives: Hyperpolarized ^{3}He magnetic resonance imaging (MRI) previously revealed the temporal and spatial heterogeneity of ventilation defects in asthmatics, but these findings have not been used in treatment studies or to guide personalized therapy. Our objective was to exploit the temporal and spatial information inherent to ^{3}He MRI and develop image processing methods to generate pulmonary ventilation temporal–spatial maps that could be used to measure, optimize, and guide asthma therapy.

Materials and Methods: In this proof-of-concept study, seven asthmatics provided written informed consent to an approved protocol and underwent spirometry and ^{3}He MRI on three occasions, each 5 ± 2 days apart. A registration and segmentation pipeline was developed to generate three-dimensional, temporal–spatial, pulmonary function maps. Briefly, ^{3}He ventilation images were segmented to generate ventilation masks that were coregistered and voxels classified according to their temporal behavior. This enabled the regional mapping of temporally persistent and intermittent ventilation defects that were normalized to the ^{1}H MRI thoracic cavity volume to generate persistent ventilation defect percent (VDP_P) and intermittent ventilation defect percent (VDP_I).

Results: ^{3}He temporal–spatial pulmonary function maps identified temporally persistent and intermittent ventilation defects. VDP_I was significantly greater in the posterior ($P = .04$) and inferior ($P = .04$) lung as compared to the anterior and superior lung. Persistent and intermittent ventilation defect percent were strongly correlated with forced expiratory volume in one second/forced vital capacity (VDP_P: $r = -0.87$, $P = .01$; VDP_I: $r = -0.96$, $P = .0008$).

Conclusions: Temporal–spatial pulmonary maps generated from ^{3}He MRI can be used to quantify temporally persistent and intermittent ventilation defects as asthma intermediate end points and targets for therapy.

Key Words: sthma; hyperpolarized ^{3}He magnetic resonance imaging; image-guided therapy; lung function; ventilation defect.

Asthma is a chronic pulmonary disease (1) characterized by acute and predominantly reversible episodes of airflow limitation and airway hyper-responsiveness that leads to airway remodeling (2,3). Currently used asthma measurements are largely dependent on spirometry measurements of airflow limitation made at the mouth. Such measurements tend to overestimate large airway constriction and underestimate small airways disease (4), and these measurements cannot regionally identify the airways responsible for airflow limitation, asthma symptoms, or control.

Currently, pulmonary imaging techniques play a minor role in the clinical diagnosis and management of asthma, although quantitative measurements of regional, structural, and functional pulmonary abnormalities (5) can be derived using a number of imaging methods. For example, x-ray computed tomography (CT) has been used to show airway remodeling and evidence of gas trapping in asthmatics (6,7). Single-photon emission computed tomography (8,9) and positron-emission tomography (10) have revealed the spatial distribution and extent of airway remodeling in asthmatics at rest and during exacerbations. Hyperpolarized noble gas magnetic resonance imaging (MRI), using either ^{3}He or ^{129}Xe, also provides a way to visualize and quantify lung regions that participate in ventilation and those that do not (11,12). Longitudinal and interventional ^{3}He MRI studies have revealed the regional and temporal nature of ventilation defects in asthma before and after provocation (exercise and methacholine) and therapy (13–15). Previous

Acad Radiol 2014; 21:1402–1410

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http://dx.doi.org/10.1016/j.acra.2014.08.002

work also showed that in asthma, ventilation defects are related to disease severity (16), CT measurements of gas trapping (17), and airway morphological abnormalities (18). Taken together, these studies suggest that in asthma, ventilation defects are related to airways disease, are regionally heterogeneous, temporally variable, and responsive to therapy and provocation (19–22). Asthma ventilation defects may be considered as therapy targets or intermediate end points as they are present in older asthmatics with more advanced or severe disease, increased indices of inflammation, and more severely remodeled airways (18).

There is enormous potential for imaging methods to improve the efficacy or cost effectiveness of asthma therapy. However until now, the presence, location, and/or variability of such defects has not yet been used to guide or interpret the efficacy of asthma therapy. The purpose of this proof-of-concept study, therefore, was to exploit the inherent temporal and spatial pulmonary function information provided by hyperpolarized ^{3}He MRI to identify temporally persistent and intermittent ventilation defects as potential targets for therapy.

MATERIALS AND METHODS

Study Design

Subjects who were 18–55 years of age, with a physician diagnosis of asthma and forced expiratory volume in 1 second (FEV_1) $\geq 60\%_{pred}$ were recruited from a tertiary care asthma clinic. All subjects provided written informed consent to a study protocol that was in compliance with the Health Insurance Portability and Accountability Act and approved by the local Research Ethics Board and Health Canada. All subjects consented to three study visits, each 5 ± 2 days apart, that took place between May 2007 and May 2008. At each visit, pre- and post-exercise challenge spirometry was performed followed by ^{1}H and ^{3}He MRI. Spirometry was performed using an *ndd EasyOne* spirometer (ndd Medizintechnik AG, Zurich, Switzerland), and FEV_1, forced vital capacity (FVC), and FEV_1/FVC were obtained according to the American Thoracic Society guidelines (23). The exercise challenge was performed according to American Thoracic Society guidelines (24). Briefly, the subject exercised (after a 2-minute warm-up) for 6 minutes on a treadmill, while inhaling compressed, room temperature dry air, at a workload which increased the heart rate to 80%–90% of the individual's age predicted maximum.

Magnetic Resonance Imaging

After spirometry, MRI was performed using a whole-body 3.0-T Excite 12.0 MR system (GE Healthcare, Milwaukee, WI), as previously described (25). Subjects were in the supine position, and all image acquisitions were performed under breath-hold conditions (15 seconds) after inspiration of a 1.0-L gas mixture from functional residual capacity (FRC). To minimize the potential for differences in the level of inspiration between imaging sessions, extensive coaching was performed before and during each imaging session. To ensure that each inhalation was performed from FRC, subjects were instructed to take two tidal breaths before inhaling the gas mixture from the 1.0-L Tedlar bag (Jensen Inert Products, Coral Springs, FL).

Hyperpolarized ^{3}He MRI static ventilation imaging was enabled using a single-channel, rigid, transmit–receive elliptical chest coil (RAPID Biomedical GmbH, Wuerzburg, DEU) as previously described (25). Hyperpolarized ^{3}He gas (30%–40% polarization) was provided by a turnkey system (HeliSpin; GE Healthcare, Durham, NC) and administered to subjects (dose, 5 mL/kg of body weight) in a $^{3}He/N_2$ mixture (25). Hyperpolarized ^{3}He MRI static ventilation images were acquired after inspiration of the hyperpolarized $^{3}He/N_2$ gas mixture using a fast two-dimensional gradient-echo sequence with the following parameters: repetition time, 4.3 milliseconds; echo time, 1.4 milliseconds; flip angle, 7°; field of view, 44 × 44 cm; matrix size, 128 × 128; slice gap, 0 mm; 14 contiguous slices; and slice thickness, 15 mm. Subsequent to hyperpolarized ^{3}He MRI, conventional ^{1}H MRI was performed during a 1.0-L breath-hold of $^{4}He/N_2$ to mimic the ^{3}He MRI breath-hold maneuver. For ^{1}H imaging, a fast spoiled gradient-recalled echo sequence was applied with the following parameters: repetition time, 4.7 milliseconds; echo time, 1.2 milliseconds; flip angle, 30°; field of view, 44 × 44 cm; matrix size, 256 × 256; slice gap, 0 mm; 14 contiguous slices; and slice thickness, 15 mm.

Image Analysis

Overview of Pipeline. Figure 1 provides a summary of the registration and segmentation pipeline used to generate whole-lung, two-dimensional, temporal–spatial pulmonary function maps. The inputs to the pipeline are N ^{3}He images acquired at visits $i \in \{1, 2..., N\}$, where $N \geq 2$, and an associated ^{1}H MR image acquired at an arbitrary visit$j$, $j \in \{1, 2..., N\}$. The pipeline consists of four steps: 1) registration, 2) ^{1}H MRI segmentation (26), 3) ^{3}He MRI segmentation (26), and 4) temporal map generation and was developed using 3D Slicer 4.2 open-source platform (http://www.slicer.org, Boston, MA) and MATLAB R2013 A (The Mathworks Inc., Natick, MA). In this proof-of-concept demonstration, ^{3}He MR images were acquired at three visits ($N = 3$), and an associated ^{1}H MR image was arbitrarily chosen at visit 2 ($j = 2$).

Step 1: Registration. As shown in Figure 1, using 3D Slicer, ^{3}He MR images acquired at each visit i, $^{3}He_{visit i}$, $i \in \{1, 2..., N\}$, and the ^{1}H MR image acquired at visit j, are coregistered to $^{3}He_{visit i = j}$ to generate temporal–spatial pulmonary function maps. $^{3}He_{visit i = j}$, corresponding to the same visit at which the ^{1}H MR image was acquired, is used