Original Investigation

Noncystic Fibrosis Bronchiectasis: Regional Abnormalities and Response to Airway Clearance Therapy Using Pulmonary Functional Magnetic Resonance Imaging

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Rationale and Objectives: Evidence-based treatment and management for patients with bronchiectasis remain challenging. There is a need for regional disease measurements as focal distribution of disease is common. Our objective was to evaluate the ability of magnetic resonance imaging (MRI) to detect regional ventilation impairment and response to airway clearance therapy (ACT) in patients with noncystic fibrosis (CF) bronchiectasis, providing a new way to objectively and regionally evaluate response to therapy.

Materials and Methods: Fifteen participants with non-CF bronchiectasis and 15 age-matched healthy volunteers provided written informed consent to an ethics board-approved Health Insurance Portability and Accountability Act-compliant protocol and underwent spirometry, plethysmography, computed tomography (CT), and hyperpolarized ^{3}He MRI. Bronchiectasis patients also completed a Six-Minute Walk Test, the St. George's Respiratory questionnaire, and Patient Evaluation Questionnaire (PEQ), and returned for a follow-up visit after 3 weeks of daily oscillatory positive expiratory pressure use. CT evidence of bronchiectasis was qualitatively reported by lobe, and MRI ventilation defect percent (VDP) was measured for the entire lung and individual lobes.

Results: CT evidence of bronchiectasis and abnormal VDP (14 ± 7%) was observed for all bronchiectasis patients and no healthy volunteers. There was CT evidence of bronchiectasis in all lobes for 3 patients and in 3 ± 1 lobes (range = 1–4) for 12 patients. VDP in lobes with CT evidence of bronchiectasis (19 ± 12%) was significantly higher than in lobes without CT evidence of bronchiectasis (8 ± 5%, $P = .001$). For patients, VDP in lung lobes with ($P < .0001$) and without CT evidence of bronchiectasis ($P = .006$) was higher than in healthy volunteers (3 ± 1%). For all patients, mean PEQ-ease-bringing-up-sputum ($P = .048$) and PEQ-patient-global-assessment ($P = .01$) were significantly improved post-oscillatory positive expiratory pressure. An improvement in regional VDP greater than the minimum clinical important difference was observed for 8 of the 14 patients evaluated.

Conclusions: There was CT and MRI evidence of structure-function abnormalities in patients with bronchiectasis; in approximately half, there was evidence of ventilation improvements after airway clearance therapy.

Key Words: Bronchiectasis; airway clearance therapy; magnetic resonance imaging; ventilation.

INTRODUCTION

Bronchiectasis, a chronic airway disease, is characterized by irreversible dilation of the airways leading to pooling and poor clearance of mucus in affected regions (1). There is considerable overlap between bronchiectasis and other chronic airway diseases such as cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD). In fact, up to 50% of patients with COPD have associated bronchiectasis and these patients have higher rates of exacerbation and worse outcomes (2,3). The increasing prevalence and clinical impact of bronchiectasis are now recognized due to their significant burden on patients of all ages and on global healthcare costs.

Evidence-based treatment and management for patients with bronchiectasis remain very challenging. The overall goal of treatment is to improve quality of life by reducing cough, sputum volume, sputum purulence, and the number of chest infections. Unfortunately, despite the increasing number of randomized controlled trials in recent years, currently there are no pharmacological treatments approved, and clinical trials struggle to achieve enrollment targets and demonstrate

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treatment effects (4,5). Despite these challenges, numerous antibiotics, mucoactive therapies, anti-inflammatory agents, and chest physiotherapy are currently under investigation (6). Regional disease measurements may be particularly important in bronchiectasis because focal distribution of disease is quite common. For example, idiopathic bronchiectasis often affects the lower lobes, immotile cilia syndrome has a right middle lobe, and lingula predominance and allergic bronchopulmonary aspergillosis typically present centrally (7). Because of this, evidence-based treatments for patients with bronchiectasis will become increasingly dependent on sensitive, objective, and regional markers of lung function in proof-of-concept trials.

Thoracic imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI) provide direct structural and functional measurements of pulmonary disease (8). Although CT is considered the most sensitive and specific method to diagnose and manage bronchiectasis, a few studies have explored the value of MRI. Pulmonary MRI, with or without the use of inhaled gas, may be performed to obtain regional measurements of lung function. In contrast to global lung measurements made at the mouth (such as spirometry), regional measurements of lung function provided by MRI may be more sensitive to disease and treatment. Such measurements have been proposed for use as intermediate end points in clinical trials of new therapies and their utility has been demonstrated in CF (9), COPD (10–12), and asthma (13,14).

To date, there have been no studies that evaluated regional ventilation using MRI in non-CF bronchiectasis. Therefore, the objective of this study was to regionally evaluate and compare bronchiectatic airways observed on CT with pulmonary ventilation using MRI in patients with non-CF bronchiectasis. We also investigated the effect of airway clearance therapy (ACT) on regional MRI ventilation measurements, providing a new way to objectively and regionally evaluate response to therapy.

MATERIALS AND METHODS

Study Subjects and Design

All subjects provided written informed consent to a published study protocol (www.clinicaltrials.gov #NCT02282202) approved by a local research ethics board and compliant with the Personal Information Protection and Electronic Documents Act (Canada) and the Health Insurance Portability and Accountability Act (USA). Male and female participants enrolled were between 45 and 85 years of age, including subjects with a clinical diagnosis of non-CF bronchiectasis (n = 15), and healthy volunteers (n = 15) with no history or diagnosis of any chronic or current acute respiratory illness. During a single visit, all subjects performed spirometry, plethysmography, and inspiratory thoracic CT within 30 minutes of MRI. Subjects with bronchiectasis underwent a second study visit 3 weeks after their initial visit to evaluate the efficacy of 4× daily oscillatory positive expiratory pressure (oPEP) device use (Aerobika, Trudell Medical International, London, Canada), as previously described (10). At pre- and post-oPEP visits, patients completed the St. George's Respiratory Questionnaire (SGRQ) (15), spirometry, plethysmography, MRI, and Six-Minute Walk Test (6MWT) (16). The Patient Evaluation Questionnaire (PEQ) (17) was completed weekly.

Pulmonary Function, 6MWT, and Questionnaires

All subjects performed spirometry (MedGraphics Corporation, St. Paul, Minnesota) according to the American Thoracic Society guidelines to quantify the forced expiratory volume in 1 second (FEV_1) and the forced vital capacity (FVC) (18). A whole body plethysmograph (MedGraphics Corporation) was used to measure lung volumes, and the attached gas analyzer was used to measure diffusing capacity of the lung for carbon monoxide (DL_{CO}). The 6MWT was performed according to the American Thoracic Society guidelines to measure the Six-Minute Walk Distance (6MWD). The SGRQ (15) and PEQ (17) were used with permission. The PEQ was previously described (17) and evaluates cough frequency, cough severity, chest discomfort, dyspnea, bronchodilator use, ease-bringing-up-sputum, and patient-global-assessment.

MRI and CT Acquisition Protocol

MRI was performed on a whole body 3.0 Tesla Discovery MR750 (General Electric Health Care, Milwaukee, WI) system. For both ^{1}H and ^{3}He MRI, subjects were instructed to inhale a gas mixture from a 1.0 L Tedlar bag (Jensen Inert Products, Coral Springs, FL) from functional residual capacity (FRC) and image acquisition was performed during a 16-second inspiration breath-hold (19). Coronal ^{1}H MRI was performed prior to ^{3}He MRI, both previously described (19).

Thoracic CT volumes were acquired with a 64-slice Lightspeed VCT system (General Electric Health Care) with subjects in breath-hold after inhalation of 1.0 L of N_2 gas from FRC as previously described (20). Using the manufacturer settings and the ImPACT CT patient dosimetry calculator (based on the Health Protection Agency [UK] NRPB-SR250), the volumetric CT dose index was 4.4 mGy and the total effective dose was 1.8 mSv. On the basis of these values and the size-dependent conversion factors of 1.00–2.00, the size-specific dose estimates, which were calculated by using the approach previously described (21), ranged from 5 to 9 mGy.

MRI and CT Image Analysis

Thoracic CT datasets were evaluated by a chest radiologist with 25 years of experience who was unaware of the subjects' clinical data. As shown in Figure 1, for all subjects, lung lobes (left lower lobe [LLL], left upper lobe [LUL], right lower lobe [RLL], right middle lobe [RML], and right upper lobe [RUL]) were evaluated for visual evidence of bronchiectasis and categorized as bronchiectasis present or absent based on