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Characterization and detection of physiologic lung changes before and after placement of bronchial valves using hyperpolarized helium-3 MR imaging: preliminary study

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Abstract

Rational and Objectives—To determine the efficacy of hyperpolarized helium-3 (HHe) ventilation and apparent diffusion coefficient (ADC) HHe magnetic resonance imaging (MRI) in detecting changes in lung function and microstructure in emphysematous lung after bronchial valve (BV) placement.

Materials and Methods—One patient diagnosed with emphysema had nine BVs placed in upper lobe bronchi. Imaging was performed pre- and 6-months post-BV placement. Coronal HHe ventilation MRI was used to assess volume changes in the ventilated portions of the lung. Coronal ADC HHe MRI, acquired with b-value pairs of 0 and 1.6 s/cm² during a second 10 s breath-hold, was used to compute ADC values.

Results—HHe ventilation MRI revealed decreased ventilation in the treated segments of the upper lobes after BV placement. Increased ventilation in the lower lobes and 2 untreated segments of the left upper lobes were also observed, with an upward shift of the major fissure of the right lung. Whole lung mean ADC decreased 6.3% from baseline: mean $\pm$ std = 0.48 ± 0.196 cm²/s to 0.45 ± 0.176 cm²/s (towards healthier values) following BV placement.

Conclusions—HHe ventilation MRI detected an increase in whole lung volume and an interlobar fissure shift indicative of increased ventilation of lower relative to upper lobes. Reduced ADC values suggest increased ventilation to healthy lower lobes at the expense of more diseased, expanded alveolar spaces in the upper lobes distal to BV placement. These results suggest that this ionizing-radiation free method for examining the lungs may offer functional and structural information useful in BV intervention planning.

Keywords

Bronchial; Valves; MR; Helium; CSI; Emphysema

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Introduction

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by chronic airflow limitation due to chronic bronchitis and emphysema, a condition marked by the progressive destruction of the alveolar walls and subsequent enlargement of the airspace. Although the upper-lobes are usually the first affected, there is considerable variability in the location and degree of emphysema. Emphysematous changes lead to a decrease in lung ventilation as air becomes entrapped within afflicted lung regions, and are the cause of dyspnea, exercise impairment, and a reduced quality of life ¹. In 2005, emphysema was deemed primarily responsible for the death of over 14,000 Americans ², and it is estimated that more than 2 million people in the United States alone are currently affected by this disease ³. Lung volume reduction surgery (LVRS) with surgical removal of the non-functioning, hyperinflated areas has been shown to be effective in patients whose emphysema predominantly involved the upper-lobes; however, the procedure is highly invasive, and is associated with high morbidity (20–30%) and mortality (7.6%) rates within 90 days post-surgery ^{4–6}.

New, less-invasive bronchoscopic approaches to treat COPD have been tested in the past decade and are currently under investigation ^{4,7,8}. These new procedures employ a variety of different devices (e.g., bronchial blockers, bronchial sealants, or one-way bronchial valves), but their basic concept is the reduction of ventilation ⁴ to the areas with the most severe emphysema, which, if atelectasis occurs, is conceptually similar to the volume loss created by LVRS but with a much less invasive procedure. The IBV Valve[®] (Spiration Inc, Redmond, WA), which is currently undergoing Phase III clinical trials in the US, is one such device for the minimally invasive treatment of patients with severe emphysema. This small one-way bronchial valve (BV) can be placed during a single bronchoscopic procedure in selected bronchi. The BV can induce atelectasis ⁸ but investigations using quantitative computed tomography (QCT) showed the most common mechanism associated with significant improvement in quality of life was a redirection of airflow to non-treated regions of the lung ⁴. Currently, multiple valves are placed bilaterally in upper lobe bronchi in patients with upper-lobe predominant emphysema ^{8,9}. Although the upper-lobes are commonly the first area to be affected, there is considerable variability in the location and degree of emphysema. The development of a clinical imaging modality that can generate high-resolution, three-dimensional functional maps of the lung without the use of ionizing radiation could provide a more targeted approach to valve placement, which could improve effectiveness.

With hyperpolarized helium-3 (HHe) MRI, the flow of air within the lung can be directly visualized and regional differences in lung ventilation can be well assessed. Also, in animal models and human studies it has been demonstrated that by measuring the displacement of the gas atoms with apparent diffusion coefficient (ADC) makes HHe MRI an excellent biomarker for emphysema, capable of detecting early structural changes ^{10–12}. HHe MRI can be done pre- and post-BV placement, enabling immediate, non-invasive assessment of the treatment and instructing consequent correction if results are unsatisfactory. Therefore, HHe MRI is a promising technique for assessing the effects of the BV in patients with emphysema. Adoption of this technique has the potential to improve patient outcomes by preserving functional lung tissue, as well as predicting patients that will respond to BV placement.

The purpose of this study was two-fold: (1) to evaluate the capability of HHe ventilation MRI in demonstrating lung ventilation patterns changes post-BV placement, and (2) to determine if ADC HHe MRI can detect microstructural differences due to the redistribution of ventilation from diseased to healthy lung regions post-BV placement.

Materials and Methods

HHe ventilation and ADC MRI and pulmonary function testing (PFT) (model PB100 spirometer, Puritan Bennett, Lenexa, KS) were performed at baseline and 6-month post BV placement in a single COPD patient who had completed the Phase III clinical trial of IBV Valves (clinicaltrials.gov identifier NCT00145548; local IRB-HSR#14031). The patient was randomized to the control arm of the parent study and after completing the 6-month trial period was eligible for BV treatment in a continued access protocol. This patient, a 73 year old female with a 40 pack/year smoking history, had nine BVs placed in airways leading to the upper lobes (five in the right lung and four in left lung, not including the lingular segments) according to the usual procedure via flexible bronchoscopy ^{4,13} (Fig. 1). Sizing of the target bronchi using a calibrated balloon catheter was performed prior to BV insertion. An inclusion criterion of the parent trial was upper lobe predominant emphysema as determined by CT and perfusion lung scan.

Each HHe MRI acquisition was performed during a breath hold following the inhalation of a mixture of approximately 500 cc of HHe (~40% polarization ^{14,15}) and 300 cc of medical grade nitrogen. The same volumes of HHe / nitrogen mixture were administered at both time points. The patient was instructed to exhale completely before inhaling the HHe gas mixture, with prior repeatability studies showed a less than 5% difference in ADC values between repeat studies ¹¹. Baseline imaging was performed on a 1.5-T Magnetom Sonata and 6-month post-BV placement imaging on a 1.5-T Magnetom Avanto (both scanners: Siemens Medical Solutions, Malvern, PA). Identical scan methods and acquisition parameters were used at the two time points. Nine contiguous coronal HHe ventilation MR slices displaying the entire lung volume were acquired in a single breath hold using a gradient recalled echo (GRE) sequence with acquisition parameters: slice thickness = 20 mm; in-plane resolution = $1.6 \times 1.6 \text{ mm}^2$; TR/TE = 6.7/2.85 ms; flip angle = 9° . ADC HHe MRI employed a GRE sequence with bipolar gradients to produce diffusion sensitization with *b*-values of 0 and 1.6 s/cm^2 and a diffusion time (Δ = 1.5ms) as previously described ¹¹. Seven contiguous coronal ADC HHe MR images (14 images, 7 for each *b*-value) were taken over a second breath-hold displaying the entire lung volume using the following parameters: slice thickness = 20 mm; in-plane resolution = $3.3 \times 3.3 \text{ mm}^2$; TR/TE = 11/6.7 ms; flip angle = 7.5° .

Pulmonary function was assessed using Forced Vital Capacity (FVC) and Forced Expiratory Volume in 1 second (FEV1) in liters. An absolute difference in FEV1 measurements between pre- and post-BV placement of greater than 0.225L was set as the limit for clinical significance, which was identified as sufficient to overcome imprecision due largely to variations in patient effort ¹⁶. Previous studies have shown that a greater than 30% reduction in lung capacity would be needed for a significantly different in spirometry measurement ¹⁷.

HHe ventilation and ADC HHe MR images were post-processed and analyzed using an image processing algorithms developed in MATLAB (The MathWorks, Natick, MA) previously described ^{10,18}. Changes in ventilation area were quantified by measuring the transverse and longitudinal dimensions of each lung in thresholded HHe ventilation images. Distinct anatomical patterns observed on the lung periphery of pre- and post-IBV placement scans were selected as reference points for each measurement to reduce biasing. Whole lung volume was determined for each condition using a general technique previously used in rabbit studies (multiplying voxel size by number of voxels above threshold) ^{10,18}. ADC HHe MR images were post-processed to include only pixels above a defined threshold (six times the standard deviation of the background noise). Mean ADC values of the whole lung (i.e. left and right combined) were computed for each slice and over all slices. ADC data from all

slices was evaluated for first quartile (Q_1), third quartile (Q_3) and interquartile range (IQR). This study was completed with approval from the IRB (International Review Board).

Results

PFT results showed no clinically significant changes in spite of blocking ventilation to 6 segments in the upper lobes. Measured FVC/FEV1 values pre- (1.94/0.67L) and post-BV placement (1.92/0.61L) were used to determine an FEV1 absolute difference (0.06L) well beneath the level of clinical significance (0.225L). The chest radiograph showed no change over the 6-months except for the addition of BVs (Fig. 1).

Comparison of HHe ventilation MR images from baseline and 6-months post-BV placement demonstrated considerable changes in the distribution of the HHe gas in the lungs (Fig. 2). The areas where the BVs were placed, in the anterior regions of the upper lobes, showed reduced ventilation after valve placement, as expected (dashed white arrows, Fig. 2). The posterior regions of the right lower lobe, left lower lobe, and left upper lobe corresponding to the untreated lingular segments showed an increase in ventilation after BV placement (solid white arrows, Fig. 2). An upward shift of the right major fissure was also apparent (gray arrows, Fig. 2), presumably due to a compensatory shift of ventilation from the treated upper lobe to the right lower lobe after the placement of the BVs in the upper lobes. A 19.5% increase in total ventilated lung volume was measured from baseline (1.28 L) to post-BV placement (1.53 L). Imaging was not performed at total lung capacity; thus, lung volume measurements were smaller than FVC. Longitudinal right lung measurements of two medial HHe ventilation images slices showed a mean percent difference of 27.2% between baseline (106.6 mm and 128.0 mm) and post-BV placement (134.5 mm and 164.1 mm). Longitudinal left and transverse lung changes were minimal.

ADC HHe maps of the lungs showed differences in diffusion in specific regions between the two time points. The average of the first three anterior lung slices revealed a 9.4% reduction in mean ADC and the elimination of areas of high ADC values in the upper lobes post-BV placement (Fig. 3). Central and posterior lung slices showed a 5.9% increase in mean ADC, apparently due to higher than normal diffusion values in newly ventilated regions of the superior segments of the lower lobes (Fig. 3). The mean ADC of the whole lung decreased 6.3% from baseline ($0.48 \pm 0.196 \text{ cm}^2/\text{s}$) to 6-months post-BV placement ($0.45 \pm 0.176 \text{ cm}^2/\text{s}$). The IQR also decreased from baseline ($0.52 \text{ cm}^2/\text{s}$; $Q_1 = 0.25 \text{ cm}^2/\text{s}$ and $Q_3 = 0.77 \text{ cm}^2/\text{s}$) to post-BV placement ($0.46 \text{ cm}^2/\text{s}$; $Q_1 = 0.26 \text{ cm}^2/\text{s}$ and $Q_3 = 0.72 \text{ cm}^2/\text{s}$) by 11.5%, which can be visualized as more uniform ADC HHe MR images (Fig. 3) and a tighter distribution of ADC values around the median (Fig. 4). Nearly identical signal-to-noise ratio (SNR) values of 28.2 and 30.1 were found for the images with b-value = $0 \text{ s}/\text{cm}^2$ (no diffusion-sensitization) for baseline and post-intervention images, respectively.

Discussion

In this single patient, we found that HHe ventilation and ADC MRI could offer insight into functional and structural changes in lung function after BV placement. The BVs were placed in bilateral upper lobe bronchi, and HHe ventilation MR images confirm the absence of ventilation to the treated segments of the upper lobes after the intervention, which demonstrated the effectiveness of the BVs in functionally excluding lung distal to the valves. This study confirms the shift of ventilation found with QCT observed in earlier studies after bilateral upper lobe treatment⁴. ADC HHe MRI results also add evidence to support that BV treated patients have significant improvement in ventilation to less diseased lung by blocking ventilation to the more diseased upper lobes⁹.

Elevations in HHe ADC have been shown to correspond to emphysematous tissue in patients with COPD ¹⁹. In this patient, the upper lobes had the largest region of elevated ADC consistent with the patient's diagnosis of upper lobe predominant emphysema. Following treatment, these areas no longer ventilated and thus no longer contributed to the measured whole lung mean ADC. It was the exclusion of these regions that likely caused the small decrease in whole lung mean ADC following treatment. Elevated ADC values observed in newly ventilated areas of the superior left lower lobe post-treatment were likely indicative of additional emphysema revealed only after these regions were allowed to ventilate fully. More normal ADC values detected in newly expanded areas of the inferior lower lobes were evidence of an increase in healthy lung tissue ventilation. An increase in the ventilation of more normal alveoli can also be inferred from the reduction in the IQR and the increased distribution of values near the mean in the ADC histogram post-BV placement. In addition, the increase in ventilated lung volume of 250 cc on HHe ventilation MRI was comparable to the average 300 cc increase determined using QCT, based on published data from a multicenter pilot study using BV ⁴.

The sequential use of conventional and HHe MRI on the same scanner may offer a significant advantage over CT by providing a convenient method for accessing both lung macrostructure and alveolar response to ventilation. In the future, low cost hyperpolarized Xe-129 may prove an even more effective contrast agent than HHe for assessing BV efficacy. The high alveolar-parenchyma-capillary diffusion coefficient of Xe-129 allows each lung phase to be assessed with a single tracer ^{20,21}. Currently, low polarization levels are a barrier to the use of Xe-129 in the clinic ²².

The availability of data from only a single patient limits assessment of HHe MRI as a clinically viable option for monitoring BV placement efficacy; however, we believe these results represent the capabilities of this technique due to comparisons with historic QCT data and the observed consistency with the treatment intentions ⁴. A second limitation of this study concerns the choice of a short time delay diffusion technique, which is indicated for measuring small diffusion lengths present in areas participating in gas exchange, but may not accurately appreciate changes in collateral ventilation. The testing of additional subjects, as well as the inclusion of short and long time diffusion techniques, will be considered upon FDA approval or the opening of another phase in the clinical trial.

In conclusion, this report of a single patient imaged before and after placement of BV for treatment of COPD shows that HHe ventilation and ADC HHe MR may provide insight into the changes in lung function due to reduced lung hyperinflation, and further study would be useful for BV response prediction, multiple time-point follow-up, and image guided valve deployment to improve effectiveness.

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Figure 1.

Frontal chest X-ray of a patient that received nine bronchial-valves, five in right lung and four in left lung (arrows). Image on the right is a magnification of the area within the dotted line on the left image showing the region of valve placement.

Figure 2.

Hyperpolarized helium-3 (HHe) ventilation MR images for nine contiguous coronal slices covering the entire lung from baseline (a–i) and 6-months post-bronchial valve placement (j–r). Solid and dashed white arrows indicate areas of increased and decreased ventilation, respectively. Gray arrows emphasize the upward shift of the right major fissure following treatment.

Figure 3.

Apparent diffusion coefficient (ADC) HHe maps for seven contiguous coronal slices covering the entire lung from baseline (a–g) and 6-months post-bronchial valve (BV) placement (h–n). ADC values (Mean $\pm$ STD) are given for each slice. Decreased and increased mean ADC values are displayed in red and green, respectively. At baseline, the anterior region of the upper lobes had markedly elevated ADC (red arrows), while in post treatment images these targeted regions showed no ventilation. The posterior region of the left upper lobe improved in ventilation following BV placement, but the ADC was noticeably elevated (green arrows). The posterior region of the right lower lobe expanded following treatment and displayed relatively normal ADC values (green arrows).

Figure 4.

Whole lung histogram overlay displaying the spread of apparent diffusion coefficient (ADC) values for baseline (dark gray) and 6-months post-intervention (light gray). The tighter distribution around the median after bronchial valve placement indicated less diseased ventilated lung.