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Hyperpolarized Helium-3 MRI of Exercise-Induced Bronchoconstriction During Challenge and Therapy

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Abstract

Purpose—To investigate the utility of hyperpolarized He-3 MRI for detecting regional lung ventilated volume (V_V) changes in response to exercise challenge and leukotriene inhibitor montelukast, human subjects were recruited with Exercise Induced Bronchoconstriction (EIB), a condition described by airway constriction following exercise leading to reduced Forced Expiratory Volume in 1 second (FEV1) coinciding with ventilation defects on hyperpolarized He-3 MRI.

Materials and Methods—13 EIB subjects underwent spirometry and He-3 MRI at baseline, post-exercise, and post-recovery at multiple visits. On one visit montelukast was given and on two visits placebo was given. Regional V_V was calculated in the apical/basilar dimension, in the anterior/posterior dimension, and for the entire lung volume. The whole lung V_V was used as an end-point and compared to spirometry.

Results—Post-challenge FEV1 dropped with placebo but not with treatment, while post-challenge V_V dropped more with placebo than treatment. Sources of variability for V_V included region (anterior/posterior), scan, and treatment. V_V correlated with FEV1/ Forced Vital Capacity (FVC) and Forced Expiratory Flow between 25%-75% of FVC and showed gravitational dependence after exercise challenge.

Conclusion—A paradigm testing the response of ventilation to montelukast revealed both a whole-lung and regional response to exercise challenge and therapy in EIB subjects.

Keywords

helium; exercise; asthma; imaging; therapy

INTRODUCTION

Exercise-induced bronchoconstriction (EIB) is often a symptom of inadequate control of asthma in patients with mild asthma that may be exacerbated by exercise, the respiration of cold dry air, or methacholine challenge (1, 2). Prior studies have evaluated the ability of montelukast, a leukotriene receptor antagonist, to protect such patients against EIB (3) using spirometry. These prior studies relied on whole-lung change in Forced Expiratory Volume in 1 second (FEV1) as the end point and, therefore, did not investigate regional obstruction or ventilation.

Spirometry, most notably FEV1, is established as a useful, simple, and inexpensive marker for evaluating lung function (4). However, spirometry in general suffers from low specificity and, as a whole-lung measure, cannot provide quantification of regional ventilation and obstruction that may be characteristic of specific disease processes in EIB, chronic obstructive pulmonary disease (COPD), and asthma. If a disease process is regionally heterogeneous, a global measure such as FEV1 may be less sensitive to subtle and/or early changes in lung function than a method that can measure regional ventilation changes.

Evaluation of regional ventilation with imaging is potentially a more specific biomarker in the investigation of obstructive pulmonary disease compared to FEV1. Several functional imaging approaches have been used to measure regional ventilation, specifically nuclear scintigraphy (5), SPECT (6) and PET (7). However, these modalities are limited by low spatial resolution, coverage, and capability for repeated studies in an exercise challenge paradigm. More recently, magnetic resonance imaging (MRI) has been applied to pulmonary imaging of asthma and other obstructive lung diseases using hyperpolarized (HP) gas contrast agents (e.g. He-3 and Xe-129) to enable repeated visualization of the ventilated air spaces without ionizing radiation (1, 8-11). Using HP gas MRI, regions of ventilation defect, indicating local regions of airway obstruction, can be directly observed before and after respiratory challenge and therapy in longitudinal scans minutes apart (1) as well as over several weeks to years (12).

In the present work, regional patterns of lung obstruction are measured using HP He-3 MRI of lung ventilation in a prospective double-blind, placebo-controlled, multi-institutional study to assess response to oral montelukast (Merck Sharpe & Dohme, Whitehouse Station, NJ) therapy in EIB. Ventilated Volume (V_V), defined as the percentage of total lung volume filled by HP He-3 gas, is used to quantify the regional response to exercise challenge with and without pre-exercise montelukast therapy in EIB.

MATERIALS AND METHODS

Human Subjects

Thirteen subjects with EIB were recruited at two separate sites (8 female, 5 male, age range 19-46 years; mean 24 ± 7 years). Six of 13 subjects were imaged at Site A, while 7 of 13 were imaged at Site B. The main inclusion criteria was a decrease in FEV1 of greater than 15% after exercise challenge on two separate days (6-8 minutes on treadmill with heart rate at 80-90% of age-predicted maximum while breathing cold, dry air). All studies were Health Insurance Portability and Accountability (HIPAA) and Institutional Review Board (IRB) compliant (H-2007-0313) and informed consent was obtained.

Study Design

Each subject participated in three imaging visits as outlined in Figure 1. Imaging was performed at the same time of day for all visits to control for potential diurnal variation in lung function. On two of the three visits each subject was given an oral placebo three hours

prior to exercise challenge, on a third visit the subject received 10 mg oral montelukast. The order of placebo or drug dosing was randomized with respect to visit number and applied in a double-blind fashion.

At each visit, baseline measurements began 30 minutes prior to dosing. Spirometry and He-3 MRI were performed (baseline, time point A), followed by administration of placebo or montelukast and a wait period of 180 minutes. To induce bronchoconstriction, the subject next underwent a 10-minute exercise challenge in the room adjacent to the MRI scanner on a series 2000 TRUE treadmill (TRUE Fitness Technology, St. Louis, MO) while breathing compressed dry ambient air, followed immediately by a second round of spirometry and He-3 MRI (challenge, time point B). The speed of the treadmill was adjusted to maintain the subject's heart rate at 80-90% of their age predicted maximum ($220 \text{ bpm} - \text{age}$). The subject was then allowed 35 minutes to recover before a final round of spirometry and MRI (recovery, time point C).

Spirometry

Spirometry was performed in accordance with American Thoracic Society Guidelines with an ndd EasyOne (ndd Medical Technologies, Andover, MA) spirometer. Measurements were taken with the subject seated in a chair directly next to the treadmill. Percent Predicted (%P) values for Forced Expiratory Volume (FEV1), Forced Vital Capacity (FVC), the ratio FEV1/FVC, and Forced Expiratory Flow Rate between 25% and 75% of volume expired (FEF25%-75%) were generated by normalizing raw values for gender, race, age, and height to their predicted values using Hankinson standard tables (4).

MR Imaging and Hardware

Site A used a 1.5 T Signa HDx GE scanner (GE Healthcare, Milwaukee, WI) with a flexible wrap single channel volume coil (IGC Medical Advances, Milwaukee, WI). Site B used a 3.0 T Signa HDx GE scanner (GE Healthcare, Milwaukee, WI) with a rigid-body single-channel volume coil (Rapid Biomedical, Columbus, Ohio). The polarization of He-3 at both sites was performed using a Heli-Spin prototype commercial polarizer (GE Healthcare Biosciences, Durham, NC) utilizing the spin-exchange optical pumping method as described in the literature (13).

A 4.5-mM dose of hyperpolarized He-3 mixed with N₂ to 1 L total volume was prepared in a tedlar bag purged of oxygen to slow T₁ relaxation. The mean polarization level of the HP He-3 dose was $10.5 \pm 2.8 \%$ at site 1, and $11.6 \pm 2.1 \%$ at site 2. The bag was delivered directly to the subjects positioned supine in the scanner and gas was inhaled from functional residual capacity (FRC) through a 1/8 inch plastic tube attached to the bag. Subjects were then instructed to hold their breath through a 16-20 second MRI acquisition. Subjects were monitored continuously for blood oxygen saturation using a pulse oximeter to assess subject safety during the anoxic breath-hold and ensure adequate recovery. To further assist respiratory recovery, oxygen was delivered via nasal cannula at 2 L/min between He-3 MR scans.

Imaging at both sites used a fast 2D gradient echo scan with the following parameters: TR/TE = 3.6/1.1 ms, 7 degree flip angle, 12-16 coronal slices sufficient to cover the lung volume, 128 square in-slice matrix acquired over a 40 cm FOV, and reconstructed to a $1.56 \times 1.56 \times 15 \text{ mm}$ voxel dimension.

Data Analysis

Statistical analysis was done using the R software package (14). Image analysis used in-house software written in MATLAB (the Mathworks, Natick, MA). The V_V was calculated

by subtracting the ventilation defect volume from total lung volume and normalizing to total lung volume, similar to the approach used by other investigators (15). Defects were identified and manually segmented (Figure 2) by two imaging scientists blinded to subject ID and visit. Proton data was not acquired for all visits at both sites, and calculations of lung volume measured on proton data acquired in a subset of subjects were found to change at each time point. Therefore, to ensure inclusion of all subjects and maintain consistency across sites, the total lung volume was instead measured directly from HP He-3 images using a semi-automated thresholding algorithm. In ventilation defected regions the lung/tissue boundary was manually drawn based on visual inspection of proton images acquired at the baseline time point only. Previous work has shown negligible inter-reader bias (2.91%) and high inter-reader agreement (0.92 intraclass correlation coefficient) for V_V (16) so the average values of whole-lung V_V across the two readers were used in this study.

To investigate the correlation of V_V with spirometric measures in EIB, postchallenge V_V at placebo was compared to spirometry metrics using a Spearman's correlation coefficient, and tested via Fisher's Z-Transform. Lung volumes in the He-3 images were then divided along the superior/inferior axis into apical, middle and basal lung regions of equal volume by voxel count in order to assess apical-to-basal variations in the V_V response to exercise challenge and treatment. Images were also divided along the coronal plane into three equal-volume anterior, middle, and posterior regions to ascertain whether gravitational dependence of response to challenge and therapy was observed.

To assess reproducibility of V_V and FEV1, Bland-Altman 95% limits of agreement (LOA) were obtained for each response separately for each of the three scans using the two placebo visits from each subject (16). To assess the effects of Montelukast on V_V and FEV1, a linear mixed-effects model (17) approach was taken. Scan (baseline, challenge, recovery) and treatment were entered as additive fixed effects, with a random intercept term for subject. The need to include a scan by treatment interaction was tested via an F-test by comparing the reduction in error sum of squares relative to the degrees of freedom. The models were fitted by maximum likelihood. Residual and diagnostic plots were obtained to assess possible violations in model assumptions and 95% confidence intervals for parameter estimates were obtained.

RESULTS

Whole Lung Comparisons

All subjects tolerated the breath-holds well and diagnostic quality images were successfully obtained at all time points on each of the three visits. No adverse effects were observed. Analysis of variance showed that radiofrequency coil type and field strength differences between sites did not have a statistically significant effect on V_V ($p = 0.34$). Three out of 13 subjects that met inclusion criteria did not demonstrate a greater than 15% average drop in FEV1 post-challenge at the placebo imaging visits but were included in the image analysis.

As summarized in Figure 3, mean whole lung post-challenge V_V at placebo of all subjects correlated well with FEV1/FVC %P ($r = .69$, $p < .001$) and with FEF 25%-75% %P ($r = .57$, $p < .01$), but V_V did not correlate significantly with FEV1 %P ($r = .35$, $p > .05$) or FVC %P ($r = -.26$, $p > .05$). The lung volume measured on imaging increased an average of $9 \pm 2\%$ post-challenge with placebo ($p = 0.002$) and $10 \pm 2\%$ with treatment ($p = 0.015$), and thus did not differ significantly between placebo and drug administration ($p = 0.91$). The measured V_V did not differ significantly across repeated placebo visits ($p > .08$), but FEV1 %P did vary significantly ($p = .04$) suggesting greater variability.

A series of He-3 MRI images of a subject with strong treatment response is shown in Figure 4. A large drop in V_V (18%) from baseline to challenge in both placebo visits is evidenced by the increased size of regions with low or absent helium signal density after exercise challenge. The post-challenge drop in V_V was only 4.0% at the drug treatment visit indicating mitigation of bronchoconstriction by montelukast. In all 3 visits for this subject, recovery of V_V was near complete 35 minutes following exercise (recovery – far right column in Figure 4).

Data summarizing treatment and placebo response for all subjects over the whole lung are summarized in Table 1 and Figure 5. The mean baseline V_V of $96.5 \pm 1.1\%$ (mean $\pm$ standard error) for placebo visits dropped 9.9% ($p < .0001$) after challenge compared to only 3.4% during treatment ($p = .05$). Similarly, the mean baseline FEV1 %P of $85.8 \pm 3.1\%$ for placebo visits dropped 17.9% ($p < 0.001$) after challenge compared to 3.2 % during treatment ($p = .19$). The t-value of the mixed effects model between placebo and treatment at challenge was 3.8 for V_V compared to 5.0 for FEV1 %P, indicating a greater effect size for FEV1 %P for montelukast therapy for these data. V_V did not fully return to baseline values at recovery with placebo ($96.5 \pm 1.1\%$ vs. $94.0 \pm 1.1\%$, $p = .03$) but did return to baseline with treatment (96.8 ± 1.3 vs. 98.6 ± 1.5 ; $p = .22$). The FEV1 %P tended to return to baseline at both placebo ($85.8 \pm 3.1\%$ vs. $82.6 \pm 1.7\%$, $p = 0.06$) and treatment ($85.9 \pm 3.3\%$ vs. $87.1 \pm 2.4\%$, $p = .61$) visits.

Regional Comparisons

There was no anterior/posterior (A/P) regional V_V dependence prior to exercise challenge ($p > .25$). However, A/P regional dependence was observed post-challenge, especially at the placebo visits. V_V was significantly higher in the anterior region compared to middle ($93.04 \pm 5.30\%$ vs. $86.08 \pm 9.14\%$, $p = 0.025$) and posterior ($93.04 \pm 5.30\%$ vs. $82.46 \pm 11.00\%$, $p < 0.01$). Moreover, the A/P gradient in V_V was maintained after treatment in the post-challenge images ($p = .05$; Figure 6).

Comparing apical, middle, and basal lung regions with the subject in the supine position in Figure 7, the V_V at baseline was lower in the basal regions compared to the upper regions ($p = .05$, V_V apex/base = $96.0 \pm 5.2 / 92.3 \pm 9.5$), but postchallenge, this difference resolved both with placebo and treatment ($p > .18$). On recovery, the apical/basilar gradient had not yet returned to baseline values with either placebo or treatment ($p > .11$).

DISCUSSION

This work represents a prospective, double-blinded, multisite controlled study comparing functional lung imaging using hyperpolarized He-3 MRI to conventional spirometry under challenge and therapy in subjects with exercise-induced bronchoconstriction. There were significant and expected decreases in V_V and FEV1 in response to exercise challenge after placebo, both of which were significantly mitigated by treatment with oral montelukast. This result is consistent with prior results demonstrating a prophylactic effect of leukotriene receptor inhibitors on EIB severity when taken prior to exercise (18). The post-challenge increase in lung volume may be attributed to dynamic hyperinflation, and has been previously noted in subjects with obstructive lung disease (19). The placebo vs. treatment t-value of FEV1 %P was greater than that of V_V . However, it should be observed that the inclusion criteria for this study was based on exercise-exacerbated drop in FEV1, introducing a potential bias in direct comparison to V_V for this population.

Interestingly, and in contrast to prior studies in asthma (20, 21), the postchallenge V_V at placebo and FEV1 %P and FVC %P correlated relatively poorly (Figure 3). However, the correlation of postchallenge V_V with FEV1/FVC %P and FEF 25%-75% %P was relatively

strong. It has been previously shown that FEV1 is controlled by two components of airway obstruction, a closure component represented by FVC, and an airflow limitation component represented by FEV1 normalized to FVC, i.e. FEV1/FVC (22). The stronger correlation of V_V with FEV1/FVC and the absence of correlation with FVC suggest that V_V in this particular population is primarily a measure of airflow limitation. The correlation of V_V with FEF 25%-75% %P further supports this conclusion and is consistent with prior studies (20). The near complete reversibility after treatment and generally poorer repeatability across placebo visits of the drop in FEV1 %P post-challenge compared to V_V suggests that spirometry is a noisier measure of ventilation than V_V . Pairing this observation with a significant difference between baseline V_V and treatment challenge V_V suggests that the defect exacerbation in this population contains an airflow limitation component to which FEV1 is not as sensitive as V_V , and which is possibly more resistant to treatment.

Imaging also allows assessment of the regional distribution of lung ventilation in response to exacerbation and therapy. The supine position of the subjects led to an expected gravitational dependence of ventilation defects in the anterior/posterior direction after exercise challenge such that V_V was observed to decrease in the posterior slices. It is interesting to note that, as for whole lung measures of V_V , the lower V_V observed in gravity dependent regions was not completely reversed with treatment (Figure 6). It is possible that the force of gravity is imposing greater airflow limitation on the posterior regions after exercise stress. This may also explain some of the discrepancies in FEV1 vs. V_V in Table 1 since the two measures are acquired in differing, upright vs. supine, postures respectively. The superior/inferior gradient in V_V observed in the baseline and recovery visits is in agreement with previous work (20) and may reflect a persistent component of obstruction such as that observed in other longitudinal studies of asthma (23).

An important limitation specific to the regional analysis of V_V is the segmentation of boundaries based on imaging planes as opposed to the anatomical boundaries between lung lobes. Although the volumetric segmentation in this analysis provides some insight, the true lobar boundaries likely better reflect the functional subunits of the lungs. Segmentation at the lobar level might therefore improve the interpretation of the regional results. Also, because this study focused on the response of the V_V measure in human subjects with and without treatment, the study design did not include a group of normal subjects. Future work will apply HP gas MRI to longitudinal studies of healthy normal subjects in comparison to asthma and EIB.

In conclusion, this work found a significant and expected decrease in V_V and FEV1 in response to exercise challenge in EIB subjects with mild asthma. Treatment response was reflected in increases in both V_V and FEV1 at 180 minutes after treatment with oral montelukast. Regionally, an anterior-to-posterior gradient of decreasing V_V after exercise challenge was observed, suggesting worsening exacerbation of EIB in gravitationally dependent lung regions. The results show the potential of using exercise challenge as a viable approach for visualizing exacerbation of asthma affected airways and regional response to montelukast with HP gas MRI.

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Figure 1. Timeline of spirometry and image acquisition (baseline, A; post-challenge, B; and recovery, C). Measures were repeated at each of three visits (2 placebo, 1 treatment).

Figure 2.
Representative coronal hyperpolarized He-3 MRI image with outlined regions indicating segmented lung volume (green boundary) and defect regions (red boundaries).

Figure 3.

Correlations between postchallenge ventilated volume and spirometric measures **(a)** FEV1/FVC, **(b)** FEF 25%-75%, **(c)** FEV1, and **(d)** FVC percent predicted (%P). The significant correlations were between V_V and FEV1/FVC ($r = 0.61$, $p < 0.05$), and between V_V and FEF 25%-75% ($r = 0.62$, $p < 0.05$).

Figure 4.

He-3 lung images from site A (Subject 8, Table 1) showing a strong V_V response to challenge and treatment. Challenge-induced defects are observable and postchallenge decreases in FEV1 for this subject coincide with decreases in V_V.

Figure 5. Response of FEV1 to (a) placebo compared with (b) montelukast treatment, and response of V_V to (c) placebo compared with (d) montelukast treatment for all 13 subjects.

Figure 6.

Anterior-posterior dependence of V_V for **(a)** placebo visits and **(b)** drug treatment visits. Boxes extend from lower to upper quartile with hashes at the median. Whiskers extend to 150% of the interquartile range of the sample. Outliers are denoted with + signs. P-values comparing region that are significant at the .05 level are indicated by an asterisk.

Figure 7.

Apical-basilar dependence of V_V for **(a)** placebo visits and **(b)** drug treatment visits. Boxes extend from lower to upper quartile with hashes at the median. Whiskers extend to 150% of the interquartile range of the sample. Outliers are denoted with + signs. P-values comparing region that are significant at the .05 level are indicated by an asterisk.

Table 1Inclusion criteria and Percent Change in V_V and FEV1 for EIB Subjects

Subject	B_0 (T)	Gender	Age	Height (cm)	% FEV1 Drop for Inclusion	Placebo Treatment				% FEV1	
						Δ FEV1 Visit1	Δ FEV1 Visit 2	ΔV_V Visit 1	ΔV_V Visit 2	Δ FEV1	ΔV_V
1	3	M	26	180	-13.2	-16.3	-10.6	-12.7	-10.6	-3.9	-11.7
2	3	M	24	172	-22.8	-14.1	-13.0	-9.8	-12.6	9	-11.4
3	3	M	21	179	-19.8	-34.5	-47.2	-17.9	-18.1	-12.4	-10
4	3	M	28	173	-16.2	-17.0	-14.7	-6.0	-10.8	-11.1	-5
5	3	F	26	154.5	-15.3	-18.8	-19.3	-13.3	-17.4	4.1	-11.3
6	3	F	21	182	-21.8	-6.1	-22.3	-11.8	-10.2	5.6	5.7
7	3	F	46	160	-35.3	-22.4	-32.7	-8.5	-11.2	-11.3	13.2
8	1.5	F	22	166.5	-35.5	-19.0	-34.2	-16.6	-18.5	-10.2	-4
9	1.5	M	19	173	-18	-19.0	-16.1	-6.1	-3.7	-7	0
10	1.5	F	22	163.5	-18.3	-11.4	-15.9	-0.6	-0.8	-8.2	-1
11	1.5	F	22	164.5	-16.4	-3.9	-29.5	-10.5	-15.1	-6.4	-5.7
12	1.5	F	20	161.5	-23.4	-5.0	-29.6	0.0	-0.9	-0.7	-0.2
13	1.5	F	20	164	-38.2	-43.6	-23.4	-13.2	-13.0	2	-2.6