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Regional Heterogeneity of Lobar Ventilation in Asthma Using Hyperpolarized Helium-3 MRI

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Abstract

Rationale and Objectives: To determine lobar ventilation patterns in asthmatic lungs with hyperpolarized ³He magnetic resonance imaging (HP ³He MRI).

Materials and Methods: Eighty-two subjects (14 normal, 48 mild-to-moderate asthma, and 20 severe asthma) underwent HP ³He MRI, computed tomography (CT) and spirometry. After registering proton to ³He images, we segmented the lungs from proton MRI and further segmented the five lung lobes (right upper lobe–RUL, middle–RML and lower–RLL; left upper–LUL and lower–LLL) by referring to the lobar segmentation from CT. We classified the gas volume into four signal intensity levels as follows: ventilation defect percent (VDP), low ventilation percent (LVP), medium ventilation percent (MVP) and high ventilation percent (HVP). The local signal

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intensity variations in the ventilated volume were estimated using Heterogeneity Score (Hs). We compared each ventilation level and Hs measured in the whole lung and lobar regions across the three subject groups.

Results: In mild-to-moderate asthma, the RML and RUL showed significantly greater VDP than the two lower lobes (RLL and LLL) ($p = 0.047$). In severe asthma, the pattern was more variable with the VDP in the RUL significantly greater than in the RLL ($p=0.026$). In both asthma groups the lower lobes (RLL and LLL) showed significantly higher HVP and Hs compared to the three upper lobes (all $p = 0.015$).

Conclusion: In asthma, the RML and RUL showed greater ventilation abnormalities, and the RLL and LLL were more highly ventilated with greater local heterogeneity. These findings may facilitate guided bronchoscopic sampling and localized airway treatment in future studies.

Keywords

Asthma; hyperpolarized gas imaging; magnetic resonance imaging; ventilation defect percent; ventilation heterogeneity

Introduction

Asthma is a chronic disease characterized by airway narrowing that leads to symptoms of wheezing, chest tightness, cough and difficulty breathing. These symptoms result from underlying chronic inflammatory processes that render the airways hyper-responsive to perturbations that in normal airways would evoke a negligible response (1). The heterogeneity of airway obstruction is now well accepted, suggesting localized disease processes including persistent and reversible regions of obstruction, both of which have been visualized using functional imaging methods (2,3).

Computed tomography (CT) imaging has been used to characterize regions of airway thickening (4) and regions of low parenchymal density at expiratory lung volume to identify air trapping (5,6). Independently, hyperpolarized helium-3 ($HP\ ^3He$) MRI has demonstrated regions of lower than normal ventilation termed “ventilation defects” (7) in asthma. Regional ventilation abnormalities have also been associated with airway disease including airway narrowing (8), air trapping and inflammation (6). $HP\ ^3He$ MRI and CT have been used in combination to compare structure-function associations between anatomical markers of airway remodeling and ventilation defects (6,9). Such regionally specific approaches show promise for better characterizing regional ventilation heterogeneity in asthma generally (2,10,11) as well as localized therapy, for example, bronchial thermoplasty (12).

Quantitative methods have improved characterization of ventilation defect percent (VDP) (13–15) as a biomarker in obstructive lung disease measured from $HP\ ^3He$ MRI. Recently several approaches using K -means (16,17) or histogram normalization (18) have enabled classification of regions of ventilation defect as well as hyper-intense signals that distinguish subjects based on presence and severity of asthma. While VDP captures the size and distribution of obstructed regions, it does not reflect the level of heterogeneity, which is a distinct feature of asthmatic lungs. A recent study (19) proposed the “heterogeneity score (Hs)” as a biomarker measured on HP gas images by computing regional signal coefficient

of variation (CoV) in the ventilated lung volume. This local ventilation heterogeneity measure has been used effectively to distinguish asthmatics from non-asthmatics after deep inspirations following a methacholine challenge (19). Another study measured the CoV of raw gas signal intensity directly in seven asthmatic subjects and found a decrease after salbutamol treatment reflecting less ventilation heterogeneity after bronchodilation (20).

These quantification methods have been validated for objective and robust whole lung (global) VDP and Hs measurements. However, the difficulty of discerning fissures on proton MR images limits the understanding of ventilation heterogeneity with respect to anatomic boundaries such as the lung lobes. The alternative method of equal-volume partition of the lungs (15,21) will necessarily intersect several anatomic lobe boundaries impairing interpretation. The advances in automated segmentation of lung lobe boundaries and in quantitative CT (qCT) measures have facilitated regional structure-function assessment of ventilation. It is now feasible to measure lung density and ventilation using qCT, VDP, and Hs biomarkers that are regionally specific and co-registered at the lobar and segmental levels (6,22,23). For example, in a small asthma cohort, ventilation defect volume was found to be larger in the right middle lobe compared to the right upper and lower lobes (6). In a methodologically similar study, ventilation defect sites in ex-smokers were spatially related to abnormal subsegmental airway morphology measured on CT (24).

The purpose of the study was to characterize HP ^3He MRI biomarkers of VDP and Hs by lung lobe with respect to asthma severity for a large population of asthmatics derived from the Severe Asthma Research Program (SARP) (25). The hypothesis of this work is that regional patterns of lobar ventilation abnormalities and heterogeneity will be greater in asthma and differ regionally by asthma severity.

Methods and Materials

Human Subjects

This study was conducted in accordance with Health Insurance Portability and Accountability Act regulations and was approved by our Institutional Review Board. Written informed consent was obtained from all subjects. Subjects were excluded if an asthma exacerbation or respiratory complication had occurred within six weeks prior to imaging or if the forced expiratory volume in one second (FEV_1) percent predicted (PP) was $< 60\%$. Excluding the more severely obstructed subjects was in accordance with the ^3He IND at the time of the study. A major factor differentiating severe from mild-to-moderate asthma was a significantly greater frequency and severity of high-risk clinical outcomes (25). ^3He was approved by the US Food and Drug Administration for inhalation as an Investigational New Drug (IND # 64,687). We recruited 82 adult subjects consecutively from 2005 to 2009 through exploratory MRI substudies affiliated with the National Heart, Lung & Blood Institute SARP. These subjects were classified as normal ($n=14$), mild-to-moderate ($n=48$), and severe ($n=20$) based on criteria presented in earlier work (25). All subjects underwent spirometry, HP ^3He MRI and inspiratory multiple detector computed tomography (MDCT) performed less than 72 hours apart.

Magnetic Resonance Imaging

Proton and HP ^3He MR imaging were each performed in the axial plane during a 16–20 second breath-hold on a 1.5T Signa HDx GE scanner (GE Healthcare, Milwaukee, WI) with broadband capabilities. Helium was polarized to 30% to 40% using a Heli-Spin prototype commercial polarizer (Polarean, Inc., Durham, NC) located adjacent to the MRI scanner.

Both proton and ^3He MRI scans were acquired at functional residual capacity plus 14% of total lung capacity (TLC), approximately 1 L of gas. In order to bring the diaphragm to a comparable position for both scans, each subject performed a breath hold after inhaling an equivalent volume of air or $^3\text{He}/\text{N}$ mixture for proton and ^3He MRI, respectively. In both cases, subjects were positioned supine and inhaled the gas through a plastic tube (inner diameter 3.2mm) attached to the bag.

The proton scan used the system's body radiofrequency-coil with a two-dimensional (2D) multislice single-shot fast spin echo sequence: repetition time (TR)/echo time (TE)=474/33 ms; field of view (FOV)=40 × 40 cm; acquisition matrix=128 × 128; echo train length=77, slice thickness=1.5 cm; 12–18 axial slices. The acquisition matrix was reconstructed to a 256 square matrix with a voxel size of 1.56 mm × 1.56 mm × 15 mm.

The ^3He scan used a fast 2D multislice gradient-echo sequence with TR/TE=7.8/4.2 ms; flip angle=7°, and acquisition matrix, FOV, slice thickness, and slice position matched to the proton images of lung anatomy. During the scan, blood oxygen saturation was monitored by means of pulse oximetry, and 100% oxygen was delivered through a nasal cannula between imaging sequences to assist respiratory recovery.

Multidetector Computed Tomography

MDCT imaging was performed at total lung capacity during an approximately 4 second breath-hold on a GE Light Speed CT scanner with 16 or 64 detectors (VCT, GE Medical Systems, Milwaukee, WI). CT acquisition and reconstruction parameters were: pitch=0.984 to 1.675; rotation time=0.5 s; source voltage=120 kV; reconstructed slice thickness=0.5 to 0.625 mm; and medium smooth “standard” reconstruction algorithm. Total effective dose ranged from 3–5 mSv depending on subject size.

Spirometry

Prior to the MRI scans, spirometry was performed with an ndd EasyOne spirometer (ndd Medical Technologies, Andover, MA) according to American Thoracic Society guidelines (26). FEV₁ and FEV₁ over forced vital capacity (FEV₁/FVC) were normalized to predicted values for gender, race, age, and height from the Hankinson standard equations (27).

Image Analysis

A comprehensive analysis of the gas images was performed by exploring the lobe dependency for four signal intensity ranges, including ventilation defect, low-, medium-, and high-ventilated regions. Specifically, VDP and Hs were compared using HP ^3He MRI across the lobar boundaries derived from inspiration CT images obtained in the same subjects.

Proton images were registered to ^3He using 3D rigid registration by Advanced Normalization Tools (ANTs) (<https://github.com/stnava/ANTs>). We segmented the right and left lungs on the registered proton using a region-growing method written in MATLAB (MathWorks, Natick, MA). Then we further segment the lung lobes (right upper –RUL, middle–RML and lower–RLL; left upper–LUL and lower–LLL) manually by drawing the fissure lines on the proton image while referring to the anatomically-matched CT slice (6).

Ventilation defects were quantified as a binary defect mask using adaptive *K*-means clustering (17) on the gas images within the proton lung mask. Whole lung VDP is calculated as the ventilation defect volume over total lung volume. Similarly, lobar VDP is calculated as the ventilation defect volume in a lobe over the corresponding lobar volume.

After ventilation defect region was determined, we extended the adaptive *K*-means method to further quantify the ventilated volume into three ventilated regions above defect region: low-ventilated region, medium-ventilated region and high-ventilated region. The details of this extension are presented in the Appendix section. In an analogous calculation to that of VDP, the regional volume of each ventilated level over the whole lung or a lobe volume yielded global or lobar low ventilation percent (LVP), medium ventilation percent (MVP), and high ventilation percent (HVP).

In addition, we also measured ventilation heterogeneity using local ventilation *H*s as previously described by Tzeng et al (19). The voxel heterogeneity index at each voxel was calculated within the ventilated volume within a specific neighborhood of the voxel while excluding both segmented defects and vasculature. The voxel neighborhood was defined as all voxels within an *L*-by-*L* block centered at this voxel and within the same slice, where *L* is 10% of the average maximum width of the left and right lungs. The voxels outside the ventilated volume were treated as undefined (i.e. NaN's). Therefore, the *H*s for each image set was computed as the average of all voxel heterogeneity index values within the entire ventilated lung volume as well as each ventilated lobe volume. The higher the heterogeneity score, the greater the local spatial variation of the observed ventilation.

To assess anterior to posterior (A/P) gravitational dependence, 3D lung volumes were reoriented to the coronal view and were divided along the A/P direction into three equal volumes (anterior, middle, and posterior). Specifically, the 2D axial images (typically $256 \times 256 \times 18$) were first reoriented to a stack ($18 \times 256 \times 256$) of 256 coronal slices with slice thickness = 1.56 mm with no gaps between slices. The lung volume at each coronal slice was calculated. We then defined the boundaries of the anterior, middle, and posterior lung regions by identifying the coronal slice position that best divided the total lung volume into thirds.

Statistical Analyses

Within each subject group, we used Wilcoxon signed-rank test to compare pairwise lobar differences in VDP, HVP and *H*s. Among the three severity groups, we used one-way analysis of variance (ANOVA) to compare lobar measurements of VDP, HVP and *H*s. Similarly, one-way ANOVA was also used to compare the global measurements, including age, spirometric measures, whole lung ventilation distribution percent (VDP, LVP, MVP and

HVP) and Hs, among three subject groups. Homogeneity of variance was tested using Levene's test. The model normality assumption was checked, and if violated, Welch's test was used to assess global effect of ANOVA. After the global effect was confirmed to be significantly different, the multiple comparison test was performed using the Tukey-Kramer procedure to control the pairwise comparisons among the severity groups jointly so as to avoid type I error rate inflation. Correlation among global measures including spirometric measures, Hs and whole lung VDP was assessed using Spearman correlation with a 95% confidence interval (CI).

The Wilcoxon signed-rank test was used to perform pairwise comparison of A/P dependence within each subject group between lobes for the three groups. A $p < 0.05$ was considered significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., NC, USA).

Results

All subjects tolerated the imaging protocol without complication or adverse events. The demographics for the subject population studied are summarized in Table 1. Subjects were older in asthma vs. normal subjects ($p < 0.026$) with generally more females than males in all groups.

Lobar Measurements and Comparison

Lobar measures of lung function are summarized in Figure 1 and 2. The pairwise lobar comparisons indicated that in the mild-to-moderate asthma group, the RML and RUL were more affected with greater VDP compared to the two lower lobes (RLL and LLL) (all $p < 0.047$, Figure 1). In severe asthma, this trend was maintained with greater average VDP increases in RML and RUL relative to the two lower lobes; however, statistically only the average increase in RUL versus RLL was significant ($p = 0.026$). In healthy normal subjects, the two upper lung lobes (RUL and LUL) were slightly but significantly more affected than the lower lobes (RLL and LLL) with all $p < 0.031$.

Overall trends in the extent of the HVP were the opposite of the pattern for VDP (Figure 2a). In both asthma groups, the HVP was significantly greater in the two lower lobes (RLL and LLL) than in the upper lobes (RUL, RML, and LUL) with all $p < 0.0056$. Additionally, these two lower lobes had greater HVP than the RML in all subject groups (all $p < 0.020$).

Similar to HVP, the average Hs was greater in the two lower lobes (RLL and LLL) compared to the three upper lobes (RUL, RML, and LUL) in asthma with all $p < 0.015$ (Figure 2b). This pattern of higher Hs in the RLL and LLL was more distinct in severe asthma. By contrast, the LLL was found significantly less heterogeneous than the RUL in the normative group ($p = 0.024$).

Comparing among the three subject groups, the average VDP in all the lung lobes tended to increase progressively from normal to severe asthma. These VDP increases were significant in the RUL, RML, RLL and LLL ($p < 0.036$) in severe asthma compared to normal subjects.

The Hs in RLL was significantly greater in severe asthma compared to both mild-to-moderate asthma and normal subjects with all $p<0.05$.

Global Measurements and Comparison

Global measures of lung function are summarized in Table 1. FEV₁ PP and FEV₁/FVC PP were lower in asthma vs normal subjects (all $p<0.005$). Both spirometric measures were similar in mild-to-moderate and severe asthma. Compared to both normal and mild-to-moderate asthma subjects, VDP and Hs were significantly greater while MVP was significantly lower in severe asthma ($p=0.042$; Table 1). When the two asthma groups were pooled, the global VDP in asthma was significantly greater than the normal ($p<0.0001$). The global VDP correlated significantly with FEV₁ PP, FEV₁/FVC PP and Hs ($p=0.0005$, Table 2). The global LVP gradually increased whereas HVP decreased progressively from normal to severe asthma (Figure 3). However, these changes did not reach statistical significance.

Typical regional parametric maps of the ventilation intensity and heterogeneity maps are shown in Figure 4 with defects at apical, middle, and basal slices color-coded by lung lobe (Figure 4a, d, and g). The corresponding ventilation distribution maps (Figure 4b, e, and h) illustrate the variations in the four ventilation regions for each subjects. Severe asthma tended to have greater defected regions in the RUL and RML (green and yellow outline), which was also revealed in group-wise comparisons (Figure 1). Typically, heterogeneity tended to be greater in severe asthma (Hs=0.31) as compared to mild-to-moderate asthma (Hs=0.24) and normal subjects (Hs=0.20) as exemplified in Figure 4c, f, and i.

Anterior/Posterior Gradient

A gravity dependence of ventilation was observed for VDP in anterior, middle and posterior lung regions (Figure 5). The VDP was significantly higher for anterior vs. middle regions in the supine position for all groups ($p=0.012$) with the A/P gradient becoming more apparent with increased asthma severity. The VDP was significantly higher in anterior vs. posterior regions in normal ($p=0.0002$) and mild-to-moderate asthma ($p=0.0010$), but not in severe asthma.

Discussion

This work provides insight into patterns of ventilation heterogeneity in asthma. In a large asthma cohort, the ventilation distribution analysis considers lobar patterns of ventilation heterogeneity in high-ventilated as well as low-ventilated lung regions. The glyph charts of lobar VDP in Figure 1 illustrate the predominant pattern of right middle and upper lobes being more affected compared to the two lower lobes (RLL and LLL). Overall, these patterns tended to be more pronounced in severe asthma, and all lung lobes tend to be more defected in severe vs. mild-to-moderate asthma.

The lobar analysis of VDP presented in the current work builds on previous work in a smaller population of asthmatics using manual segmentation of ventilation defect volume by lung lobe (6). The previous work also found regional differences in defect volumes by lung lobe, and especially higher defect volumes in the RML compared to RUL and RLL regions. With the larger sample size in the current study this pattern of greater VDP in the RML is

confirmed and we observed the tendency that both the RUL and RML are more defected than the lower lobes (RLL and LLL) in asthma.

The patterns of obstruction observed here and in other studies may reflect a variety of possible underlying causes from airway remodeling to inflammation, mucus plugging and smooth muscle tone. These phenomena are possibly occurring in the same individual at different locations in the lungs. Prior work has confirmed associations between ventilation defect regions and some of these processes in asthma. For example, structural changes in the central airways, measured as increased wall thickening and reduced lumen area on CT imaging, have been observed proximal to ventilation defect regions (9), and localized inflammation, measured as higher granulocyte counts in bronchiolar lavage drawn from a specific lung lobe, have been confirmed at locations of greater ventilation defect volume in asthma (6).

The strength of the pattern suggests that the consequences of chronic disease processes in asthma are more pronounced for the RUL, LUL, and RML, possibly due to the greater branch angle or eccentricity of the feeding airways to these lung regions. These results suggest that in asthma the upper lobes are more prone to ventilation defects and may serve as early indicators of disease progression; potentially, the right middle and upper lobes may be prioritized in image-guided bronchoscopic assessment or therapy. However, the meaning of this pattern of lobar ventilation distribution is not entirely clear. Additionally, LUL is measurably more defected than LLL but this VDP difference was not statistically significant. This implies that the right lung may be more affected than the left lung in asthma. A possible reason for the right/left differences might lie in the relative volumes of the lung lobes. For example, the LUL being of generally larger volume may provide more capacity to offset the local compliance differences that lead to the higher VDP observed in the RUL and RML. Further study is needed to evaluate whether the observed ventilation heterogeneity eventually progresses to significantly greater values of VDP across both right and left upper lobes in patients with severe asthma. Confirmation of these cross-sectional patterns and their longitudinal change will be further assessed in our ongoing longitudinal studies in severe asthma (25).

Local ventilation heterogeneity maps (Figure 4) reflect a characteristic pattern in our study. The central portions of each of the three ventilated regions in the ventilation map tend to be homogeneous, whereas the transition areas between two different ventilated regions appear to be more heterogeneous. The Hs measure excludes ventilation defect sites such that a more defected lobe may counterintuitively have a relatively low heterogeneity. While the upper lobes (RML, RUL and LUL) were more defected, the lower lobes (RLL and LLL) possibly responded by demonstrating more hyperventilated regions with greater heterogeneity given that a fixed volume of gas is inhaled for each dose. The lobe comparison in the asthma cohort suggested the two lower lobes had greater local heterogeneity and higher HVP than the three upper lobes. Regionally, Hs in RLL is the only lobar measure that distinguished severe asthma from normal and mild-to-moderate asthma. Taken together, upper lobe ventilation deficiency and increased lower lobe (RLL and LLL) heterogeneity with greater HVP may be an indicator of asthma and its progression.

Several global results in this work reinforce previous studies. The examples of parametric maps (Figure 4) show that, while normal subjects may have scattered small peripheral defects, severe asthma tends to have larger, more focal defects and diminished highly ventilated regions relative to mild-to-moderate asthma. These are consistent with the finding that more extensive defects are a characteristic of moderate to severe disease (7). In contrast to spirometric measures, global VDP distinguished severe asthma (6.5%) from both normal (1.2%) and mild-to-moderate asthma (3.4%) subjects, which is in agreement of previous findings (7,14,28–30) that HP gas MRI is more sensitive or predictive of disease exacerbations than spirometry and VDP associates with the severity of obstructive pulmonary disease. The shift to higher VDP together with greater local ventilation heterogeneity in primarily severe disease may be a reflection of specific characteristics of more severe asthma.

A gravity dependent ventilation pattern was also observed in our study, in agreement of previous studies (21,23). It is worth noting that this anterior-posterior gradient continues to hold with the progression of asthma, whereas it was found to decrease in chronic obstructive pulmonary disease (COPD) (31). Future work will test the dynamics of the A/P gradient by comparing images of ventilation pre and post-bronchodilation. While regional ventilation abnormalities were found to become more homogeneously distributed during COPD progression (23), in our asthma cohort, ventilation patterns became more heterogeneous with disease severity. There is also evidence that the temporal characteristics of gas wash-in and wash-out from high- and low-ventilated regions differs in severe vs. mild-to-moderate asthma (32), possibly indicating more spatially variable differences in lung compliance due to regionally variable airway injury and remodeling.

There are several limitations of this study. One is the relatively small severe asthma sample size ($N = 20$) compared to mild-to-moderate asthma ($N = 48$). This may contribute to statistical bias that may miss significant patterns, particularly in the more severe asthma group. Similarly, there is a more moderate degree of global obstruction for the severe asthma subjects in this study than is typical; this is due to safety concerns at the time of the study such that the patterns observed here may not reflect the general severe asthma population. However, from another perspective the difference in patterns observed for the asthma severity groups studied here may be an indication of the strength of the signal from imaging even in a relatively mild group of severe asthmatics. Future work will assess these patterns in severe asthmatics with representatively low lung function, pre- and post-bronchodilator to reveal reversibility, and longitudinally over a 3 year period (33). In addition, the CT protocol and reconstructions were standardized and protocol adherence was better enforced for subsequent phases of SARP. This more recent data are being analyzed for regional correspondence between MRI and CT measures in a comparably sized population. Instead of manual lobe delineation, the automated CT analysis and lobe segmentation via a deformable registration between CT and proton MRI (22) is ongoing and will be used in future studies.

In conclusion, the regional quantification of baseline pulmonary ventilation distribution in asthma with HP gas MRI reveals severity-related regional heterogeneity patterns. The comprehensive evaluation of the static ventilation distribution including both regions of ventilation defect and well-ventilated regions may provide a more complete understanding

of the most common disease sites as well as less vulnerable control sites. Our results suggest the right middle and upper lobes may be more prone to ventilation defects, whereas the lower lobes (RLL and LLL) exhibited comparatively greater measures of hyperventilation and local heterogeneity. These findings suggest that lobe-specific monitoring of asthma progression may improve understanding of progression and help guide localized airway treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Ventilated volume was determined by excluding the detected defect volume and the estimated vascular volume from the total lung volume. As an extension of the adaptive K -means clustering (17), we continue to use the low-intensity-signal percentage P_L , which is calculated from the whole-lung histogram, to ultimately guide the identification of three ventilated clusters. A larger P_L value reflects likely more defected lungs with less high-intensity gas voxels.

To define the 3 ventilated clusters, the ventilated volume was first classified into five clusters ($V_i, i = 1, 2, \dots, 5$) by K -means with uniformly-distributed initial cluster centers. Then the second (V_2) and fourth (V_4) of these five clusters were further classified into 5 sub-clusters ($V_{ik}, k = 1, 2, \dots, 5$). Based on the P_L value, these ventilation clusters were then combined into three levels of ventilated regions as illustrated in Figure A.1. For severe-diseased lungs ($P_L \geq 10\%$), the first two clusters (V_1 and V_2) were determined as low-ventilated region immediately above the ventilation defect region and the last two sub-clusters of the fourth cluster (V_{44} and V_{45}) together with the fifth cluster (V_5) were grouped as the high-ventilated region. For non- and mild-diseased lungs ($P_L < 10\%$), the first cluster (V_1) and the first two sub-clusters of the second cluster (V_{21} and V_{22}) together were collected as low-ventilation region and the last two clusters (V_4 and V_5) were defined as high-ventilation region. In either case, the clusters in between low- and high-ventilation regions were marked as medium-ventilated region. The reproducibility of this extended quantification of ventilation distribution was evaluated using the exercise-induced bronchoconstriction study cohort (17) that includes 6 subjects with each imaged at two separate visits.

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Figure 5.

Bar graph of anterior/posterior (A/P) regional dependence in three subject groups. An A/P gradient, with the anterior region more defected than both middle and posterior regions was observed in all subject groups, and this trend became more pronounced with increased asthma severity. Values are means for all subject groups and error bars are $\pm$ standard deviation.

Figure 1.

Glyph charts of average lobar ventilation defect percent (VDP) in the normal group (left), mild-to-moderate asthma (middle) and severe asthma (right). The shaded regions in light colors (right upper lobe (RUL) in green, right middle lobe (RML) in yellow, right lower lobe (RLL) in cyan, left upper lobe (LUL) in magenta, left lower lobe (LLL) in red) represent the volume of each lobe as a percentage of total lung volume. The shaded regions in the corresponding bold colors represent the average VDP values of individual lobes in a subject group. In each glyph chart, the symbols *, #, and § denote significant differences found in the other lobes compared to the RUL, RML and LUL respectively. A $p < 0.05$ was considered significant.

NOTE: this figure should be printed in color.

Figure 2.

Bar graphs of a) high ventilation percent (HVP) and b) heterogeneity score (Hs) in lung lobes with error bars representing standard deviation. The lobar HVP showed the lower lobes (RLL and LLL) contained more highly ventilated regions relative to the upper lobes in the two asthma groups. The lobar Hs suggested the two lower lobes had more heterogeneity relative to the upper lobes (RML, RUL and LUL). In each bar graph, the symbols *, #, and § denote significant differences found in the other lobes compared to the RUL, RML and LUL respectively. A $p < 0.05$ was considered significant.

Figure 3.

Boxplot of percent ventilation distribution in normal, mild-to-moderate, and severe asthma groups. For each subject type, ventilation defect percent (VDP), low ventilation percent (LVP), medium ventilation percent (MVP), and high ventilation percent (HVP) were measured from the gas images within the proton lung mask for a complete ventilation analysis. Boxes extend vertically between the 25th and 75th percentiles, the whiskers extend to the most extreme data that are not considered outliers, and outliers are plotted with plus sign, circle and diamond for normal, mild-to-moderate and severe asthma groups. The central mark represents the median.

Figure 4.

Examples of segmented defects and the corresponding ventilation maps at apical, middle, and basal slices of three subjects. Columns from left to right show apical, middle and basal lung slices of a subject. Row a, d, and g show the segmented defects (right upper lobe (RUL) in green, right middle lobe (RML) in yellow, right lower lobe (RLL) in cyan, left upper lobe (LUL) in magenta, left lower lobe (LLL) in red) in a normal subject, mild-to-moderate asthma, and severe asthma respectively. Row b, e, and h show the corresponding ventilation maps, which contain four ventilation levels: ventilation defect percent (VDP) in red, low-ventilated percent (LVP) in orange, medium-ventilated percent (MVP) in green and highly ventilated percent (HVP) in blue, at the same slices of the same normal, mild-to-moderate, and severe asthmatic subjects. Row c, f, and i display the corresponding heterogeneity maps.

Normal: 21-year-old male, percent predicted forced expiratory volume in 1 s (FEV₁ PP) = 90%, VDP = 0.5%, LVP = 14.7%, MVP = 63.1%, and HVP = 21.7%, heterogeneity score = 0.20. Mild-to-moderate asthmatic: 19-year-old male, FEV₁ PP = 72%, VDP = 2.7%, LVP = 15.5%, MVP = 60.2%, and HVP = 21.6%, heterogeneity score = 0.24. Severe asthmatic: 53-year-old male, FEV₁ PP = 86%, VDP = 9.5%, LVP = 34.7%, MVP = 49.2%, HVP = 6.7%, heterogeneity score = 0.31.

NOTE: this figure should be printed in color.

Table 1

Subject demographics and global functional measurements for normal and asthmatic subjects

	Asthma				Significance of difference (<i>p</i> value)	
	Normal (N = 14)	Mild-to-moderate (N = 48)	Severe (N = 20)	Normal vs Mild-to-moderate	Normal vs Severe	Mild-to-moderate vs Severe
Age years	21±3	31±12	38±14	0.026	0.0005	0.095
Male/Female	5/9	22/26	7/13	-	-	-
FEV ₁ PP (%)	102±12	89±14	79±19	0.0014	0.0002	0.058
FEV ₁ /FVC PP (%)	100±6	89±10	87±15	0.0050	0.0039	0.79
Whole lung VDP (%)	1.2±1.3	3.4±3.6	6.5±7.3	0.23	0.0034	0.033
Whole lung LVP (%)	16.1±4.4	19.1±7.3	21.6±8.8	0.37	0.087	0.42
Whole lung MVP (%)	61.6±3.4	58.9±5.6	54.9±8.3	0.27	0.0062	0.042
Whole lung HVP (%)	21.1±4.5	18.6±6.2	17.0±18.4	-	-	-
heterogeneity score (-)	0.24±0.029	0.24±0.030	0.27±0.043	0.91	0.034	0.014

Values are expressed as mean ± standard deviation. FEV₁ PP: percent predicted forced expiratory volume in 1 second; FVC: forced vital capacity; VDP: ventilation defect percent; LVP: low ventilation percent; MVP: moderate ventilation percent; HVP: high ventilation percent. A *p*<0.05 was considered significant. The pairwise comparison was performed and reported only if the global effect of one-way analysis of variance (ANOVA) was confirmed to be significantly different.

Table 2

Spearman correlation between ventilation defect percent (VDP) and other global measures including FEV₁ PP and FEV₁/FVC PP from spirometry and heterogeneity score

	Spearman Correlation		
	ρ	p	95% Confidence Interval
VDP vs. FEV ₁ PP	-0.38	0.0005	[-0.55, -0.17]
VDP vs. FEV ₁ /FVC PP	-0.42	<0.0001	[-0.58, -0.22]
VDP vs. Heterogeneity score	0.68	<0.0001	[0.54, 0.78]

A $p < 0.05$ was considered significant.