Measures of Ventilation Heterogeneity Mapped with Hyperpolarized Helium-3 (HHe-3) MRI Demonstrate a T2-High Phenotype in Asthma

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Abstract

Background: HHe-3 MR is a non-invasive imaging method which maps and quantifies regions of ventilation heterogeneity (VH) in the lung. VH is an important feature of asthma, but little is known as to how VH informs patient phenotypes. Purpose: To determine if VH indicators quantified by HHe-3 MRI predict phenotypic characteristics and map to regions of inflammation in children with problematic wheeze/asthma. Methods. Sixty children with poorly-controlled asthma underwent HHe-3 MRI, including 22 with bronchoalveolar lavage (BAL). The HHe-3 signal intensity defined four ventilation compartments. The non-ventilated and hypoventilated compartments divided by the total lung volume defined a VH index (VHI %). Results: Children with VHI % in the upper quartile had significantly greater airflow limitation, bronchodilator responsiveness, blood eosinophils, expired nitric oxide (FeNO), and BAL eosinophilic/ neutrophilic granulocyte patterns compared to children with VHI % in the lower quartile. Lavage return from hypoventilated bronchial segments had greater eosinophil % than from ventilated segments. Conclusion: In children with asthma, greater VHI % as measured by HHe-3 MRI identifies a severe phenotype with higher type 2 inflammatory markers, and maps to regions of lung eosinophilia. Listed on ClinicalTrials.gov (NCT02577497).

Abbreviations

BAL bronchoalveolar lavage

CT computerized tomography

FeNO Fraction expired nitric oxide

FEV_1 forced expired volume in one second

FEV_1/FVC forced expired volume in one second/forced vital capacity

FVC forced vital capacity

HHe-3 hyperpolarized helium-3

GINA Global Initiative for Asthma

ICS inhaled corticosteroids

LABA long-acting beta agonists

MCID Minimal clinically important difference

MR magnetic resonance

MRI magnetic resonance imaging

Vdef % ventilation defect percent

VH ventilation heterogeneity

VHI % ventilation heterogeneity index percent

VVI % ventilated volume percent

Author Contributions

W. Gerald Teague, MD: Study design, senior clinician-investigator, protocol development aind implementation, recruitment, clinical oversight, data analysis.

Jaime Mata, PhD: Oversight of hyperpolarized gas preparation and administration, technical leadership in administering gas and imaging sequence protocols, day to day involvement in study conduct and participant safety.

King Qing, PhD: Study design, technical co-leadership in administering gas, oversight of imaging sequence protocols, day to day involvement in study conduct and participant safety.

Nicholas J. Tustison, PhD: on-line image analysis, invented platform for quantifiyng lung volume compartments based on on He-3 signal intensity.

John P. Mugler III PhD: Senior investigator for image development, sequencing, and process, oversight of day to day image acquistion and quality.

Craig H. Meyer, PhD: development of spiral pulse sequences and image reconstruction.

Y. Michael Shim, MD: Medical leadership of hyperpolarized noble gas research program, developed quality and safety standards, input on study design.

Kristin Wavell: Lead study coordinator, responsible for study adaptation, identification and intervention into episodes of poor asthma control and exacerbations, central role in data acquisition and secure storage, regulatory official.

Talissa Altes MD: Senior investigator, critical input into study design and implementation.

Introduction

Inhaled hyperpolarized noble gases emit a signal detectable by MR which maps the distribution of gas in the trachea-bronchial tree and regions of gas exchange [1-2]. In patients with asthma, hyperpolarized gases distribute unevenly in the lungs. Regions with dark, attenuated, He-3 signal are commonly referred to as "ventilation defects" [3-6]. Ventilation defects are attributed to eosinophilic inflammatory debris and narrowing of the airways. Ventilation defects increase in size with exercise and methacholine-induced bronchoconstriction [7-8], and decrease in size post-albuterol inhalation [7,9]. Lung regions with ventilation defects localize to regions of air trapping mapped with multidetector CT in adults with asthma [10]. We previously reported that the ventilation defect % (Vdef %) was greater in children with severe compared to mild asthma, and correlated with poor symptom control and the magnitude of airflow limitation measured with spirometry [11]. In adults with severe asthma, the Vdef % positively predicted the number of past exacerbations [12].

Although regional variations in the pattern of inflammation are likely in asthma, little is known as to whether inflammed regions have greater VH. Fain and colleagues [10] found increased neutrophils in BAL from lung regions with ventilation defects and air trapping. We previously reported an adolescent with severe asthma wherein the proximal bronchial segment to a lobe with ventilation defefects had greater epithelial injury and infiltration of eosinophils compared to a segment to a ventilated lobe [13]. The Vdef% decreases following acute albuterol treatment in adults with asthma, but in the sub-group with sputum eosinophilia, the improvement

in VH is relatively less [14]. Mucus plugs identified by multidetector CT in adults with asthma correspond to sputum eosinophilia and production of eosinophil peroxidase-mediated oxidants [15]. However, studies based on sputum analysis are limited in so far as the precise regional source of expectorated sputum cannot be identified.

To address these questions, a sample of children with problematic wheeze/asthma underwent hyperpolarized He-3 (HHe-3) MRI. The investigations had two purposes: 1) to study in cross-section whether the magnitude of VH could differentiate phenotypic characteristics, and 2) whether areas of regional hypoventilation map to segments with greater granulocyte infiltration.

Methods

The study sample included 60 children with treatment-refractory wheeze/asthma referred to a university-based specialty clinic serving a mixed urban-rural population in central Virginia. Enrollees underwent a HHe-3 lung MRI within eight weeks of characterization procedures adapted from the NIH/NHLBI Severe Asthma Research Program [16]. Participants were treated according to GINA guidelines[17] by an asthma specialist for a minimum of three months before severity assignment [18]. Details regarding recruiting procedures and characterization[16], treatment [17,19], and indications for bronchoscopy [19] have been published previously.

Inclusion criteria included ages 3-17 years, diagnosis of problematic wheeze (n = 11) or confirmed asthma (n= 49) based on change in FEV_1% [?] 12% from baseline post-bronchodilator (BD), and/or a previous positive methacholine bronchoprovocation test, and treatment for a minimum of three months with [?]1 asthma controllers. Inadequate control was defined according to an asthma control test (ACT/cACT) <20, 2 or more exacerbations in the year prior to enrollment, and/or persistent airflow limitation ($FEV_1/FVC < 90^{th}$ % predicted) [20]. Exclusion criteria included premature birth < 36 weeks gestation, inability to cooperate with the MRI procedures, and significant non-asthmatic diagnoses including cardiac disease, cystic fibrosis, and a documented lower respiratory infection within six weeks of the enrollment visit. Study participation required informed consent and protocols were approved by the University of Virginia Institutional Revew Board (IRB# 157200 and #18422). The study was listed on ClinicalTrials.gov (NCT02577497).

Hyperpolarized Helium-3 Lung MRI Procedures

Children underwent a standard imaging protocol with safety monitoring under IND 57866. Images were obtained without sedation using a 1.5-T commercial whole-body scanner (Avanto, Siemens Medical Solutions, Malvern PA) and either a flexible, vest-shaped chest radio frequency (RF) coil (Clinical MR Solutions, Brookfield, WI) or a fixed geometry RF coil (Rapid Biomedical, Rimpar, Germany) tuned to the He-3 resonant frequency. Details of the MR acquisition procedures have been published previously [11] and are described in detail in the E-Supplement methods.

Bronchoscopy and BAL Procedures

Twenty-two children with therapy-resistant, inadequately-controlled asthma had clinically-indicated bronchoscopy with bronchoalveolar lavage (BAL) and assessment of air space and blood inflammatory markers two weeks following HHe-3 MRI. Samples were shared between the clinical and research laboratories under protocols approved by the University of Virginia Institutional Review Board (IRB # 17555, IRB # 19180, and IRB # 10905). A detailed description of the clinical pathway and methods for bronchoscopy and BAL has been published previously[19].

To compare granulocyte constituents in BAL from lung segments with and without visible ventilation defects, 13 children underwent MR image-guided BAL in bronchial segments to lobes with and without visible ventilation defects. The images were reviewed by a pediatric radiologist (TAA) in advance, lobes with and without ventilation defects were identified for BAL in the main bronchial segments or sub-segments accordingly. Fresh BAL was submitted to the cytopathology laboratory and examined for total and differential cell count using manual procedures. Paired BAL aliquots were labeled 1 and 2 for cytospin preparation of smears for differential cell counts, done in triplicate, by a cytopathologist blinded to the ventilation status of

the segment from which the sample was obtained. Safety of the bronchoscopy procedures has been reported previously with no unexpected major adverse events[19, 22].

Data Analysis

Four volume compartments were defined from the formatted gray-scale MRI images according to a previously published analysis platform (see E-supplement) [11, 21]. VH indicators included the Vdef % (non-ventilated volume/total lung volume), and the VHI % (non-ventilated +hypoventilated volume/total lung volume).

To examine whether the magnitude of VH informed clinical features, the sample was stratified into three sub-groups according to the quartile distribution of the VHI %. Sub-group one, mild VH, was $< 25^{th}$ %ile VHI %, sub-group two, moderate VH, middle 25^{th} -75^{th} %ile, and sub-group three, severe VH, was $> 75^{th}$ %ile. Between sub-group comparisons among scaled and categorical variables are described in the E-supplement. BAL granulocyte patterns were defined as isolated eosinophilia, isolated neutrophilia, mixed granulocytic, and pauci-granuolocytic based on published criteria [19, 23]. A p value of $< .05$ was used to refute the null hypothesis.

Results

Sixty children had detailed characterizations with MRs, including 22 who underwent diagnostic bronchoscopy. The mean sample age was 9.9 ± 3.9 years (Table I). Most were male (63%), 1/2 reported non-white racial/ethnic backgrounds. Seventy-five % had cACT/ACT scores [?] 19, 51% had [?] 1 asthma-related hospital admissions in the past year. More than 84% reported treatment with [?] 2 asthma controller medications, 50% with ICS doses [?] 800 mcg/day fluticasone equivalents. A pre-BD FEV_1/FVC % < 90%, was found in 47%. Increased serum IgE to [?] 1 allergens was detected in 80%, and 60% were sensitized to [?] 4 allergens. Eosinophilia, defined by [?] 300 eosinophils/ul blood, was present in 50%.

HHe-3 MRI Lung Volume Compartments and VH Indicators

For the total sample (n=60) the four volume compartments (E-supplement Table E-1) included the non-ventilated volume (2.8 % total volume), hypoventilated volume (16.4 % total volume), ventilated volume (27.8% total volume) and well-ventilated volume (53% total volume). Indices of VH included the Vdef % (1.29 +- 3.13), the VHI %, (17.59 +- 13.36) and the VVI % (82.40 +- 13.36). The VHI % and VVI % had Gaussian distributions, but not the Vdef % (E-supplement Figure E-1).

To examine whether volume sub-compartments varied significantly in children with greater VH, sub-volumes were compared according to the distribution of the VHI % (Figure 1). The non-ventilated and hypoventilated compartments were significantly higher, whereas the well-ventilated compartment was significantly lower, in children with VHI % values in the upper 25^{th} %ile compared to the lower 25^{th} %ile and the middle 25^{th}-75^{th} %iles. Thus, greater VH was accompanied by greater non-ventilated and hypoventilated lung volumes, lower well-ventilated volume, but no significant change in the ventilated volume compartment.

Phenotypic Features Compared According to VHI % Quartiles

Children with VHI % in the upper quartile had phenotypic features unique from those in children in the lower quartile (Table I and Figure 2). Children with VHI % in the upper 75^{th} %ile had greater non-white racial/ethnic backgrounds (73% vs 20%, p = .006), more lifetime ICU admissions (range of 0-6 vs 0-4, p = .04), and were treated with twice the number of daily controller medications (4.0 vs 2.0 , p = .02) compared to children in the lower 25^{th}%ile.

Accordingly, children with VHI % in the upper 75^{th}%ile had reduced lung function with greater airflow limitation and bronchodilator responsiveness compared to children in the lower 25^{th} %ile (Table I). Differences included lower pre-BD FEV_1 % (80 vs 100, p = .02), and lower pre-BD FEV_1/FVC % (83 vs 94, p = .04) in children with the upper 25^{th} %ile VHI %. Both the pre- and post-BD FEF_{25-75} % (55 vs 89 and 61 vs 91, respectively, $p < .05$ for both) were less than mid-flows in children with VHI % in the lower 25^{th} %ile. Furthemore children with VHI % in the upper 75^{th} %ile had overall greater bronchodilator reversibility, and the % change in the FEV_1 % from baseline was higher in the 75th versus 25^{th}-75^{th} %iles (22 vs 11, p = .01).

VHI % sub-groups likewise had difference in the magnitude of type 2 inflammatory markers (Table I). Children with VHI % in the 75th %ile had higher absolute eosinophil counts (620 cells/ ul vs 220 cells/ ul blood, p = .001), a higher proportion with absolute eosinophil counts [?] 300 cells/ul blood (87% versus 20%, p = .001) and higher FeNO (36 ppb vs 22 ppb, p = .03) compared to lower %iles. VHI % sub-groups did not differentiate total IgE and the number of positive specific IgE tests. Overall correlations between VH indicators and scaled outcomes were modest to poor (See E-supplement, results and Table E-2).

BAL Constituents

BAL total cell count, % eosinophils and % neutrophils were not significantly different among the VHI % sub-groups (Table II). However categorical granulocyte patterns did vary significantly. The proportion of children with pauci-granulocytic BAL was lower, 17%, in upper 75th %ile VHI % than it was in the the 25th-75th %ile (67%) and the 25th %ile (75%, p = .04).

In 13 children who underwent paired image-directed BALs, eosinophil counts/100 cells (Figure 3) were significantly higher (p = .04) in BAL from bronchial segments in lung regions with visible ventilation defects (7 +- 9 %) compared to regions without visible ventilation defects (3 +- 2 %). There was no difference in the percentage of BAL macrophages, lymphocytes, or neutrophils between lobes with and without ventilation defects. There were no significant differences among VHI % sub-groups in the presence of pathogenic bacteria or viruses (Table II, and E- Supplement, results).

Discussion

Children with problematic wheeze/asthma and significant VH, identified by VHI % in the upper 75th %ile, had a severe clinical phenotype with greater airflow limitation, bronchodilator reversibiity, and markers of type 2 inflammation. BAL from bronchial segments to lobes with ventilation defects had greater eosinophils, and children with VHI % in the upper 75th %ile accordingly had greater eosinophilic and neutrophilic BAL granulocyte patterns compared to children in the lower 25th %ile. These results indirectly support an important role of eosinophilic debris and type 2 inflammations in the formation of regions of hypoventilation in asthma. The results also show that the VHI %, which defines both the non- and hypoventilated volume compartments in asthma, is likely a better predictor of disease severity in asthma compared to the traditional indicator, the Vdef %.

Original studies in patients with asthma based on hyperpolarized gas MRI used ventilation defect counts as estimates of VH[3-4,6-7]. Recently, analytic platforms[5,11-12,14] were developed which quantified the Vdef % as a fraction of the total lung volume. In a previous report[11] in children with moderate to severe asthma, the median Vdef % was 1.3%, identical to the Vdef % in the present study. In this and previous reports, the Vdef % is skewed towards smaller values in a non-Gaussian distribution; hence we substituted the VHI % as an alternate VH metric to differentiate clinical features in the present study. The VHI % is normally distributed and overall performed better than the Vdef % as a predictor of clinical outcomes. However, both the VHI % and the Vdef % are global indicators of net VH in the lung, and vary significantly by anatomic region. A limiting factor in using total lung VH as a primary outcome to test treatment effects and exacerbations is insensitivity to regional differences in response which could be missed by a total lung indicator.

The results of the present study are among the first that we can find which resolve localized patterns of lung granulocytic inflammation in asthmatics based on visible ventilation defects. BAL return from lung lobes with ventilation defects had greater eosinophils. These results diverge slightly from those of Fain et al based on analysis of regional air trapping and BAL constituents in adults with asthma[10]. In that study, the absolute number and percentage of BAL neutrophils correlated with lung defect volume. The recent findings of Dunican et al based on CT identify a relationship between luminal obstruction with mucus plugs and sputum eosinophilia in adults with asthma [15].

The present study sample has co-morbid features which limits its generalizability to a broad asthma population. We would expect that the degree of VH in a community-based sample might be less than in the present study, enriched in children with severe asthma and inadequate symptom control. We studied a relatively

young sample, whereby past studies have shown greater VH in older patients with asthma[5]. We therefore would recommend future studies using hyperpolarized noble gas imaging with uniform image acquisition sequences at controlled lung volumes at several centers. This has been done in a limited way with testing the effects of bronchial thermoplasty on VH in asthma with promising early results [24].

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Tables

Table I Features of Children with Problematic Wheeze/Asthma Compared According to VHI % Dispersion

Age (years) ¤
Asthma Duration (years)
Male sex n (%) **

Table I Features of Children with Problematic Wheeze/Asthma Compared According to VHI % Dispersion

Non-white race n (%)												
Body Mass Index (kg/m^2)												
BMI % predicted												
Obese n (%)												
ACT/cACT												
Hospital Admissions												
ICU Admissions												
# Controller Meds												
Daily ICS Dose												
Pre-BD FEV_1 %												
Post-BD FEV_1 %												
[?] FEV_1 % post-BD												
Pre-BD FVC %												
Post-BD FVC %												
[?] FVC % post-BD												
Pre-BD FEV_1/FVC %												
Post-BD FEV_1/FVC %												
Pre-BD FEF_{25-75} %												
Post-BD FEF_{25-75} %												
Geometric Mean Total IgE (IU/ml)												
# + specific IgE tests [?]												
Highly Sensitized n (%)												
Absolute Blood Eosinophils (cells/μl) ᵅ												
Blood Eosinophilia ([?] 300 cells/μl) n (%)												
Expired NO (ppb)												
α mean ± SD; ** column %; p = .006, [?] p = .09 compared to mild VH; u p =.06; p = .04 compared to mild VH; p = .												

Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	T I B C s C p A c i t V % D
Total Cell and Granulocyte Counts	Total Cell and Granulocyte Counts	Total Cell and Granulocyte Counts	Total Cell and Granulocyte Counts	Total Cell and Granulocyte Counts	Total Cell and Granulocyte Counts	Total Cell and Granulocyte Counts	Total Cell and Granulocyte Counts	Total Cell and Granulocyte Counts	Total Cell and Granulocyte Counts	Total Cell and Granulocyte Counts	Total Cell and Granulocyte Counts	T C a C u c C

Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	T I B C s C p A c i t V % I
Constituent	Constituent	Constituent	Mild VH 25th %ile	Mild VH 25th %ile	Mild VH 25th %ile	Mod. VH 25th-75th %ile	Mod. VH 25th-75th %ile	Severe VH 75th %ile	Severe VH 75th %ile	Severe VH 75th %ile	Total	T
Sample n	Sample n	Sample n	4	4	4	12	12	6	6	6	22	2
Total Cell Count (X 10^6)	Total Cell Count (X 10^6)	Total Cell Count (X 10^6)	1.44 ± 1.44	1.44 ± 1.44	1.44 ± 1.44	1.47 ± 3.62	1.47 ± 3.62	1.14 ± 2.35	1.14 ± 2.35	1.14 ± 2.35	1.17 ± 1.58	1 ± 1
Eosinophils (%)	Eosinophils (%)	Eosinophils (%)	0 ± 2	0 ± 2	0 ± 2	0 ± 0	0 ± 0	1 ± 8	1 ± 8	1 ± 8	0 ± 2	0 2
BAL eosinophils [?] 1% n (%)	BAL eosinophils [?] 1% n (%)	BAL eosinophils [?] 1% n (%)	1 (25)	1 (25)	1 (25)	2 (17)	2 (17)	3 (50)	3 (50)	3 (50)	6 (27)	6 (
Neutrophils (%)	Neutrophils (%)	Neutrophils (%)	5 ± 4	5 ± 4	5 ± 4	4 ± 15	4 ± 15	15 ± 32	15 ± 32	15 ± 32	5 ± 18	5 1
BAL neutrophils [?] 6 % n (%)	BAL neutrophils [?] 6 % n (%)	BAL neutrophils [?] 6 % n (%)	1 (25)	1 (25)	1 (25)	3 (25)	3 (25)	4 (67)	4 (67)	4 (67)	8 (36)	8 (
Lymphocytes (%)	Lymphocytes (%)	Lymphocytes (%)	3 ± 3	3 ± 3	3 ± 3	3 ± 4	3 ± 4	1 ± 8	1 ± 8	1 ± 8	3 ± 3	3 3
Macrophages (%)	Macrophages (%)	Macrophages (%)	68 ± 26	68 ± 26	68 ± 26	72 ±32	72 ±32	58 ± 40	58 ± 40	58 ± 40	68 ± 37	6 3
Epithelial cells (%)	Epithelial cells (%)	Epithelial cells (%)	21 ± 25	21 ± 25	21 ± 25	12 ± 23	12 ± 23	21 ± 23	21 ± 23	21 ± 23	20 ± 25	2 2

Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	T I B C s C p A c i t V % I
Granulocyte Categories *	Granulocyte Categories *	Granulocyte Categories *	Granulocyte Categories *	Granulocyte Categories *	Granulocyte Categories *	Granulocyte Categories *	Granulocyte Categories *	Granulocyte Categories *	Granulocyte Categories *	Granulocyte Categories *	Granulocyte Categories *	Granulocyt Categories *
Isolated Eosinophilia	Isolated Eosinophilia	Isolated Eosinophilia	0	0	1 (8)	1 (8)	1 (8)	1 (8)	1(17)	1(17)	1(17)	2
Isolated Neutrophilia	Isolated Neutrophilia	Isolated Neutrophilia	0	0	2 (17)	2 (17)	2 (17)	2 (17)	2 (33)	2 (33)	2 (33)	4 (
Mixed Granulocyte	Mixed Granulocyte	Mixed Granulocyte	1 (25)	1 (25)	1 (8)	1 (8)	1 (8)	1 (8)	2 (33)	2 (33)	2 (33)	4 (
Pauci-granulocytic	Pauci-granulocytic	Pauci-granulocytic	3 (75)	3 (75)	8 (67)	8 (67)	8 (67)	8 (67)	1 (17)	1 (17)	1 (17)	1 (
Potential Lower Respiratory Pathogens ∝	Potential Lower Respiratory Pathogens ∝	Potential Lower Respiratory Pathogens ∝	Potential Lower Respiratory Pathogens ∝	Potential Lower Respiratory Pathogens ∝	Potential Lower Respiratory Pathogens ∝	Potential Lower Respiratory Pathogens ∝	Potential Lower Respiratory Pathogens ∝	Potential Lower Respiratory Pathogens ∝	Potential Lower Respiratory Pathogens ∝	Potential Lower Respiratory Pathogens ∝	Potential Lower Respiratory Pathogens ∝	P I P p t ∝
		25^{th} %ile	25^{th} %ile	25^{th}-75^{th} %ile	25^{th}-75^{th} %ile	25^{th}-75^{th} %ile	75^{th} %ile	75^{th} %ile	75^{th} %ile	Total	Total	T
Sample n	Sample n	11	11	21	21	21	9	9	9	41	41	4
Pathogenic bacteria n (%)	Pathogenic bacteria n (%)	1 (9)	1 (9)	8 (38)	8 (38)	8 (38)	2 (22)	2 (22)	2 (22)	11 (27)	11 (27)	1 (
+ Virus PCR n (%)	+ Virus PCR n (%)	4 (36)	4 (36)	9 (43)	9 (43)	9 (43)	2 (22)	2 (22)	2 (22)	15 (37)	15 (37)	1 (

Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	T I B C s C p A c i t V % I
+ Bacteria/viruses	+ Bacteria/viruses	0	0	5 (24) **	5 (24) **	5 (24) **	0	0	0	5 (12)	5 (12)	5 (
Lipid Laden Macrophage Index (range 0-5) Median	Lipid Laden Macrophage Index (range 0-5) 0 ± 0	Lipid Laden Macrophage Index (range 0-5) 0 ± 0	Lipid Laden Macrophage Index (range 0-5) 0 ± 0	Lipid Laden Macrophage Index (range 0-5) 0 ± 0	Lipid Laden Macrophage Index (range 0-5) 0 ± 0	Lipid Laden Macrophage Index (range 0-5) 0 ± 0	Lipid Laden Macrophage Index (range 0-5) 0 ± 3	Lipid Laden Macrophage Index (range 0-5) 0 ± 3	Lipid Laden Macrophage Index (range 0-5) 0 ± 3	Lipid Laden Macrophage Index (range 0-5) 0 ± 0	Lipid Laden Macrophage Index (range 0-5) 0 ± 0	Lipid Laden Macrophag Index (0 0

Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	T I B C s C p A c i t V % D
References*[19,23]; isolated eosinophilia [?] 1% eosinophils, and < 6% neutrophils; isolated neutrophilia [?] 6% neutrophils and 0% eosinophils; mixed granulocytic [?] 6% neutrophils and [?] 1% eosinophils; paucigranulocytic < 6% neutrophils and 0% eosinophils; p =	References*[19,23]; isolated eosinophilia [?] 1% eosinophils, and < 6% neutrophils; isolated neutrophilia [?] 6% neutrophils and 0% eosinophils; mixed granulocytic [?] 6% neutrophils and [?] 1% eosinophils; paucigranulocytic < 6% neutrophils and 0% eosinophils; p =	References*[19,23]; isolated eosinophilia [?] 1% eosinophils, and < 6% neutrophils; isolated neutrophilia [?] 6% neutrophils and 0% eosinophils; mixed granulocytic [?] 6% neutrophils and [?] 1% eosinophils; paucigranulocytic < 6% neutrophils and 0% eosinophils; p =	References*[19,23]; isolated eosinophilia [?] 1% eosinophils, and < 6% neutrophils; isolated neutrophilia [?] 6% neutrophils and 0% eosinophils; mixed granulocytic [?] 6% neutrophils and [?] 1% eosinophils; paucigranulocytic < 6% neutrophils and 0% eosinophils; p =	References*[19,23]; isolated eosinophilia [?] 1% eosinophils, and < 6% neutrophils; isolated neutrophilia [?] 6% neutrophils and 0% eosinophils; mixed granulocytic [?] 6% neutrophils and [?] 1% eosinophils; paucigranulocytic < 6% neutrophils and 0% eosinophils; p =	References*[19,23]; isolated eosinophilia [?] 1% eosinophils, and < 6% neutrophils; isolated neutrophilia [?] 6% neutrophils and 0% eosinophils; mixed granulocytic [?] 6% neutrophils and [?] 1% eosinophils; paucigranulocytic < 6% neutrophils and 0% eosinophils; p =	References*[19,23]; isolated eosinophilia [?] 1% eosinophils, and < 6% neutrophils; isolated neutrophilia [?] 6% neutrophils and 0% eosinophils; mixed granulocytic [?] 6% neutrophils and [?] 1% eosinophils; paucigranulocytic < 6% neutrophils and 0% eosinophils; p =	References*[19,23]; isolated eosinophilia [?] 1% eosinophils, and < 6% neutrophils; isolated neutrophilia [?] 6% neutrophils and 0% eosinophils; mixed granulocytic [?] 6% neutrophils and [?] 1% eosinophils; paucigranulocytic < 6% neutrophils and 0% eosinophils; p =	References*[19,23]; isolated eosinophilia [?] 1% eosinophils, and < 6% neutrophils; isolated neutrophilia [?] 6% neutrophils and 0% eosinophils; mixed granulocytic [?] 6% neutrophils and [?] 1% eosinophils; paucigranulocytic < 6% neutrophils and 0% eosinophils; p =	References*[19,23]; isolated eosinophilia [?] 1% eosinophils, and < 6% neutrophils; isolated neutrophilia [?] 6% neutrophils and 0% eosinophils; mixed granulocytic [?] 6% neutrophils and [?] 1% eosinophils; paucigranulocytic < 6% neutrophils and 0% eosinophils; p =	References*[19,23]; isolated eosinophilia [?] 1% eosinophils, and < 6% neutrophils; isolated neutrophilia [?] 6% neutrophils and 0% eosinophils; mixed granulocytic [?] 6% neutrophils and [?] 1% eosinophils; paucigranulocytic < 6% neutrophils and 0% eosinophils; p =	References*[19,23]; isolated eosinophilia [?] 1% eosinophils, and < 6% neutrophils; isolated neutrophilia [?] 6% neutrophils and 0% eosinophils; mixed granulocytic [?] 6% neutrophils and [?] 1% eosinophils; paucigranulocytic < 6% neutrophils and 0% eosinophils; p =	[illegible]

Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	Table II BAL Constituents Compared According to VHI % Dispersion	T I B C s C p A c i t V % I

Figure Legends

Figure 1. Violin plots showing the probability distribution of lung volumes according to the quartile distribution of the VHI % in children with problematic wheeze/asthma. In A), the non-ventilated compartment was significantly greater in children with VHI % in the upper quartile, and in B) the hypoventilated compartment likewise was significantly higher. In C) the ventilated compartment volume was not significantly different among the VHI % quartiles, however in D) the well-ventilated compartment was significantly lower in children with VHI % in the upper quartile compared to children with VHI % in the lower quartile.

Figure 2. Representative HHe-3 images from children with mild, moderate, and severe ventilation heterogeneity. The VHI % located below each image was derived from the non-ventilated and hypoventilated volume divided by the total lung volume. Regional maps of the lung volume compartments are indicated by a color labeling algorithm. The table compares phenotypic features that were significantly ($p < .05$) different in children with VHI % in the upper quartile compared to children in the lower quartile.

Figure 3. Within subject analysis of granulocyte counts/hpf in BAL return from ventilated and non-ventilated lung regions in 13 children with asthma. Ventilation status of a lung region was determined according to the presence or absence of visible ventilation defects on HHe-3 lung MRI. The plots are probability density functions and paired counts of A) macrophage, B) lymphocyte, C) eosinophil, and D) neutrophil numbers according to regional ventilation status.

Figures

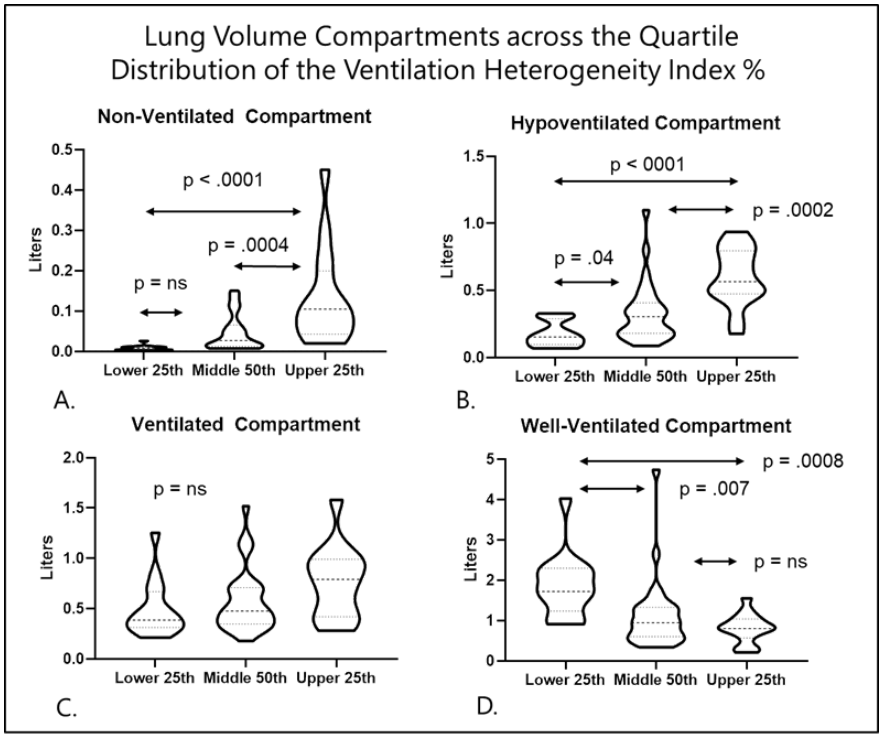
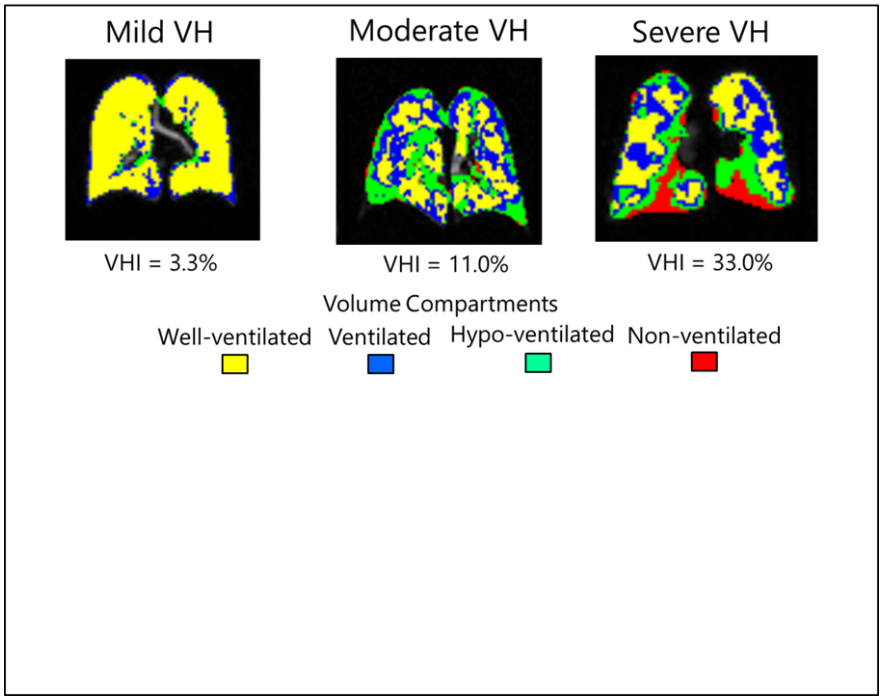


Figure 1.



Feature * p < .05	Mild VHI %ile	Moderate VHI % ile	Severe VHI %ile
Non-white race	20%	53%	73%
# Controller meds.	2	2	4
Pre-BD FEV_1 /FVC	94 %	89 %	83 %
Absolute eosinophils	220/µl	285/µl	620/µl
Expired NO	22 ppb	19 ppb	36 ppb
Pauci-granulocytic BAL	75%	67%	17%

Figure 2.

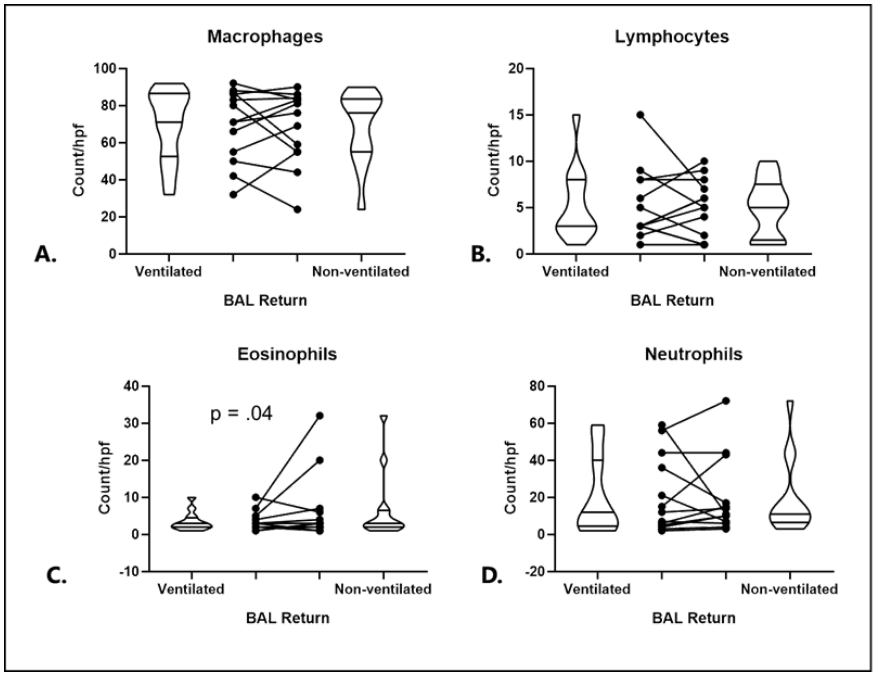


Figure 3.