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¹²⁹Xe MRI as a measure of clinical disease severity for pediatric asthma

Nancy Y. Lin, MD, MS, David J. Roach, PhD, Matthew M. Willmering, PhD, Laura L. Walkup, PhD, Md Monir Hossain, PhD, Priyanka Desirazu, M.S.E., B.E, Zackary I. Cleveland, PhD, Theresa W. Guilbert, MD, MS, Jason C. Woods, PhD

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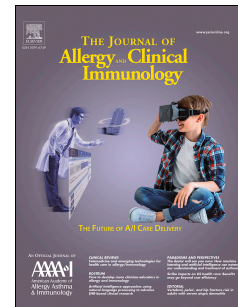
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Name	Highest Academic Degree(s)	Institutional affiliations
Nancy Y. Lin	MD, MS	1. Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
David J. Roach	PhD	1. Center for Pulmonary Imaging Research, Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 2. Department of Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Matthew M. Willmering	PhD	1. Center for Pulmonary Imaging Research, Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 2. Department of Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Laura L. Walkup	PhD	1. Center for Pulmonary Imaging Research, Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 2. Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio 3. Department of Biomedical Engineering, University of Cincinnati College of Engineering and Applied Science, Cincinnati, Ohio 4. Department of Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Md Monir Hossain	PhD	1. Division of Biostatistics & Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 2. Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio
Priyanka Desirazu	M.S.E., B.E.	1. Center for Pulmonary Imaging Research, Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 2. Department of Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Zackary I. Cleveland	PhD	1. Center for Pulmonary Imaging Research, Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 2. Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio 3. Department of Biomedical Engineering, University of Cincinnati College of Engineering and Applied Science, Cincinnati, Ohio 4. Department of Radiology, Cincinnati Children's

		Hospital Medical Center, Cincinnati, Ohio
Theresa W. Guilbert	MD, MS	1. Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 2. Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio
Jason C. Woods	PhD	1. Center for Pulmonary Imaging Research, Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 2. Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio 3. Department of Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

E-mail addresses of co-authors:

Nancy Y. Lin	Nancy.Lin@cchmc.org
David J. Roach	David.Roach@cchmc.org
Matthew M. Willmering	Matthew.Willmering@cchmc.org
Laura L. Walkup	Laura.Walkup@cchmc.org
Md Monir Hossain	MD.Hossain@cchmc.org
Priyanka Desirazu	Priyanka.Desirazu@cchmc.org
Zackary Cleveland	Zackary.Cleveland@cchmc.org
Theresa W. Guilbert	Theresa.Guilbert@cchmc.org
Jason C. Woods	Jason.Woods@cchmc.org

Corresponding author:

Name: Jason C. Woods, PhD

Address: 3333 Burnet Avenue, MLC 2021, Cincinnati, OH, USA 45229.

Telephone number: (513) 803-4463

Fax number: (513) 803-0724

Email Address: Jason.Woods@cchmc.org

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26 The authors declare the following financial interests/personal relationships which may
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Nancy Y. Lin	Dr. Lin reports grants from Cincinnati Children's Hospital Medical Center during the conduct of this study.
David J. Roach	Dr. Roach has nothing to disclose.
Matthew M. Willmering	Dr. Willmering has nothing to disclose.
Laura L. Walkup	Dr. Walkup has nothing to disclose.
Md Monir Hossain	Dr. Hossain has nothing to disclose.
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38 **Abstract**

Background: Measurement of regional lung ventilation with hyperpolarized ^{129}Xe magnetic resonance imaging (^{129}Xe MRI) in pediatric asthma is poised to advance our understanding of disease mechanisms and pathophysiology in a disorder with diverse clinical phenotypes. ^{129}Xe MRI has not been investigated in a pediatric asthma cohort.

Objective: We hypothesized that ^{129}Xe MRI is feasible and can demonstrate ventilation defects that relate to and predict clinical severity in a pediatric asthma cohort.

Methods: Thirty-seven children (13 severe asthma, 8 mild/moderate asthma, 16 age-matched healthy controls) aged 6-17 years-old were imaged with ^{129}Xe MRI. Ventilation defect percentage (VDP) and image reader score were calculated and compared to clinical measures at baseline and at follow-up.

Results: Children with asthma had higher VDP ($p=0.002$) and number of defects per image slice (defects/slice) ($p=0.0001$) than children without asthma. Children with clinically severe asthma had significantly higher VDP and number of defects/slice than healthy controls. Children with asthma who had higher number of defects/slice had higher rate of healthcare utilization ($r=0.48$, $p=0.03$) and oral corticosteroid use ($r=0.43$, $p=0.05$) at baseline. ROC analysis demonstrated the number of defects/slice and VDP were predictive of increased healthcare utilization, asthma and severe asthma. VDP correlated with FEV_1 ($r=-0.35$, $p=0.04$) and FEV_1/FVC ratio ($r=-0.41$, $p=0.01$).

Conclusion: ^{129}Xe MRI correlates with asthma severity, healthcare utilization, and oral corticosteroid use. As delineation of clinical severity is often difficult in children, ^{129}Xe MRI may be an important biomarker for severity, with potential to identify children at higher risk for exacerbations and improve outcomes.

Key Words

Asthma; pediatric; hyperpolarized MRI; spirometry; clinical severity; exacerbations; healthcare utilization;

Abbreviations: MRI: magnetic resonance imaging; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; IOS: impulse oscillometry; LCI: lung clearance index; ACT: Asthma Control Test; CT: Computed tomography; VDP: ventilation defect percentage; ^{129}Xe MRI: hyperpolarized xenon-129 magnetic resonance imaging; TLC: total lung capacity; FRC: functional residual capacity; OCS: oral corticosteroids; HCU: healthcare utilization; EMR: electronic medical record.

Clinical Implications: ^{129}Xe MRI is a safe, non-invasive and non-ionizing technique that can safely quantify regional functional defects of the lungs and may identify those at higher risk for exacerbations.

Capsule Summary: This is the first study to compare ^{129}Xe MRI in a pediatric asthma cohort. We demonstrate that ^{129}Xe MRI correlates with asthma severity, healthcare utilization, and oral corticosteroid use.

Introduction

Asthma is the most common chronic respiratory disease in children, affecting 5.5 million children in the United States (1-3). Pediatric asthma is distinctly different from adult asthma, with less-persistent symptoms but higher exacerbation frequency (4-7). Earlier and more sensitive methods of detecting subclinical physiologic changes in children with asthma are needed to prevent irreversible loss of function and decrease healthcare burden.

Spirometry, namely forced expiratory volume in one second (FEV₁) and FEV₁/forced vital capacity (FVC) ratio, is reliably used to monitor clinical disease progression in adults, but many children have difficulty performing the test. Further, normal or near normal lung function in children with asthma has often been described in literature (4, 6, 8-12). Impulse oscillometry (IOS) is another non-invasive technique to assess obstruction in the large and small peripheral airways, but can be limited by patient cooperation (13, 14). Measurement of lung clearance index (LCI) can represent a global index of gas mixing abnormality of the lungs, and has mainly been used in research settings to date (15). The Asthma Control Test (ACT) is a patient-reported metric of short-term asthma control; while its reliability and validity have been proven, it is not a robust predictor of long-term control (16-18). Computed tomography (CT) has been studied in adult asthma to evaluate the relationship between airway mucus plugs and airway obstruction, but this structural information only provides a surrogate measure for true lung function, and longitudinal CT-based studies pose nontrivial risks due to serial exposure to ionizing radiation (19, 20). While other diagnostic tests (e.g. blood eosinophil count, specific allergen testing, and flexible bronchoscopy) are used

clinically to characterize and phenotype asthma, none offer information about regional ventilation differences (21, 22).

Previous studies in adult asthma using hyperpolarized helium-3 magnetic resonance imaging (^3He MRI) demonstrated the number of ventilation defects in asthma subjects correlated with disease severity, as defined by clinical symptoms and spirometry (23). Furthermore, ventilation defect percentage (VDP) measured by ^3He MRI has been shown to be a possible predictor of asthma stability in adult severe asthma (24). ^3He MRI has been shown to be safe in pediatric subjects with mild asthma and has demonstrated increased number of, and larger regions of ventilation defects in children with asthma (25, 26). As a result of global shortage of ^3He , hyperpolarized xenon-129 magnetic resonance imaging (^{129}Xe MRI) has been increasingly studied in adults and children with obstructive pulmonary diseases such as cystic fibrosis and has been shown to predict disease outcome and measure treatment efficacy (27-30). ^{129}Xe MRI studies in adults with asthma have demonstrated significant differences in VDP, number and size of defects between subjects with mild/moderate asthma and severe asthma (23). ^{129}Xe MRI has also been used to guide bronchial thermoplasty treatment in an adult cohort, which demonstrated reproducibility of measurement of ventilation abnormalities and segmental variability (31). No ^{129}Xe MRI studies have been performed to date, however, in a pediatric asthma cohort.

We hypothesized that ^{129}Xe MRI is feasible and can demonstrate ventilation abnormalities that predict clinical severity and outcomes in a pediatric cohort with asthma.

Methods

Subject Recruitment:

Subjects aged 5-18 (mean age=11.6 ± 3.3 years-old) were enrolled from the Pulmonary, Allergy, and Pediatrics clinics at Cincinnati Children's Hospital Medical Center (CCHMC) in Cincinnati, Ohio. Subjects with asthma were sorted into two severity groups based on National Asthma Education and Prevention (NAEPP) guidelines (32). There were 13 subjects with severe asthma (NAEPP Step 5-6) and 8 subjects with mild/moderate asthma (NAEPP Step 1-4), in addition to 16 healthy control subjects.

Subjects were enrolled if they had clinical diagnosis of asthma confirmed by either a) beta-agonist reversibility of $FEV_1 \geq 10\%$ predicted, b) a positive methacholine challenge test or, c) documentation of asthma diagnosis in the past 12 months. Subjects were excluded if they could not cooperate with the imaging process; had active chronic systemic diseases, other than asthma or allergy; had known severe airway anatomic abnormalities; were within four weeks of asthma-related hospitalization or emergency department (ED) visit; had positive pregnancy test; or had personal history of cigarette or e-cigarette use. Healthy control subjects were enrolled if they did not have pre-existing pulmonary disease. They were excluded if they had baseline pulse oximetry of less than 90% on room air; had positive pregnancy test; were unable to cooperate or tolerate the imaging; or had standard MRI exclusions (e.g. metal implants). All subjects were screened for MRI safety by study personnel and medical safety by the study physician. See Online Repository for details of study visit.

This study was approved by the Institutional Review Board at CCHMC and via USFDA investigational new drug approval (IND#123,577). Written consent was

obtained from a parent or legal guardian and assent for children ≥ 11 years-old at the study visit.

Spirometry and Inhalation Dose:

Pre-bronchodilator spirometry results were collected from electronic medical records (EMR) from the most recent clinical visit for asthma subjects. For control subjects, same-day spirometry was performed immediately prior to MRI using a handheld, portable spirometer (Koko, nSpire, Longmont, CO). Spirometry was performed according to American Thoracic Society (ATS) guidelines and interpreted using population reference spirometry values from the Global Lung Initiative (GLI) spirometric prediction equations (33, 34).

Xenon Dose Administration:

Inhalation dose of hyperpolarized ^{129}Xe was $1/6^{\text{th}}$ of the subject's predicted total lung capacity (TLC) calculated using subject height from the ATS plethysmography-based guidelines for children (mean predicted TLC = 3.7 ± 1.1 liter, mean dose volume = 0.62 ± 0.18 liter, maximum allowed dose = 1 liter) (35). Xenon gas was administered by trained study staff in the presence of a medical professional. Subjects were coached to fully inhale to TLC and then resume several tidal breaths before inhaling the hyperpolarized ^{129}Xe gas mixture from functional residual capacity (FRC), followed by breath-hold (up to 16 seconds) during ^{129}Xe ventilation imaging.

Imaging Methods:

Subjects were imaged on a commercial 3T Philips Achieva[®] MRI scanner (Philips Healthcare, Best, Netherlands) and ^{129}Xe ventilation MR images were acquired using a

homebuilt, dual-loop ^{129}Xe coil. Isotopically enriched xenon (86% ^{129}Xe -enriched, Linde Specialty Gases) was polarized to approximately 40% using a commercial polarizer (Polarean® 9820, Durham, NC). After conventional ^1H locator scans (details in Online Supplement), a small calibration dose (~200 mL) of hyperpolarized ^{129}Xe gas was administered via a breath-hold maneuver to optimize the ventilation acquisition parameters. Hyperpolarized ^{129}Xe ventilation images were obtained after subjects inhaled isotopically-enriched (86% ^{129}Xe), hyperpolarized ^{129}Xe gas using a 2D gradient-echo pulse sequence, covering the entire lungs, during a breath-hold. Hyperpolarized ^{129}Xe ventilation images were acquired using a slice-selective gradient recalled echo sequence (parameters: repetition time 8.0 milliseconds (ms), echo time 4.0ms, flip angle 10-12°, field of view 300 x 300 millimeters (mm), voxel size $\approx 3 \times 3 \times 15\text{mm}$). Heart rate and oxygen saturation level were monitored with pulse oximetry throughout the study to assess safety and tolerability.

Image Analysis:

^{129}Xe ventilation images were manually segmented based on ^1H images and processed using custom semi-automated software in MATLAB (Mathworks®, Natick, MA). Lung ventilation defect calculations were performed by evaluating the percentage of voxels with signal intensity <60% threshold of the mean total lung signal, which defined the ventilation defect percentage (VDP) (36). This threshold represents our estimate of the visually-accurate defect selection and maximizes contrast compare to healthy controls, according to a previous study (36).

Blinded reader score was independently completed by two readers experienced in hyperpolarized gas MRI and ventilation defect analysis (DR, JW) after a training

session. During the training session, each reader was provided with a set of training ^{129}Xe ventilation images, ^{129}Xe ventilation images for analysis and a score sheet to record results and discuss. ^{129}Xe ventilation images were then scored independently for the number (number of defects per image slice), location (peripheral, hilar, mixed), shape (wedge, mixed) and size of ventilation defect ($\geq 3\text{cm}$, $< 3\text{cm}$). The results were totaled by the study investigator (NL), and the two reader scores were averaged and divided by number of image slices to produce the final number used for analysis.

Outcome Variables:

The primary outcomes were ^{129}Xe VDP and image reader score. EMR review for clinical outcomes was completed on March 1, 2020 to minimize potential biases introduced by altered healthcare utilization (HCU) behavior caused by the COVID-19 pandemic. Twelve of 21 (57.1%) subjects with asthma did not have complete 12-month follow-up data.

Clinical measures of baseline (12 months leading up to MRI) and follow-up (up to 12 months after MRI) asthma characteristics and severity were obtained from EMR review, including: ACT score, number of asthma-related hospitalizations, number of asthma-related ED or urgent care (UC) visits, and number of courses of oral corticosteroids (OCS). The baseline spirometry measurements (FEV_1 , FEV_1/FVC ratio) were collected from EMR from the most recent clinical visit prior to the MRI (mean time: 57 ± 61 days). The follow-up spirometry measurements were collected from clinical visits within 12 months after the MRI (231 ± 136 days). Baseline ACT scores from all clinic visits 12 months prior to MRI date and follow-up ACT scores within 12 months after MRI date were averaged to produce mean ACT score at baseline and follow-up.

The number of courses of OCS and the number of asthma-related ED or UC visits totaled over the baseline or follow-up period were divided by the number of months of follow-up for comparison. HCU was defined by any asthma-related hospitalization or ED/UC visits in the baseline or follow-up period.

Data Analysis:

All variables were tested for normality. Comparisons for two or more groups were made by student's *t*-test or Wilcoxon rank test, or one-way analysis of variance. The Tukey-Kramer method was used to adjust for multiple comparisons between groups. The associations between any two variables were examined by Pearson (for normally-distributed data) or Spearman (for non-normally distributed or categorical data) correlation, and later by multivariable linear or logistic or negative-binomial regression methods to adjust for the effects of potential confounders. Potential confounders included within the statistical models were BMI, sex, race, asthma severity and baseline clinical outcomes. All reported results are univariate linear or logistic or negative-binomial regression models since confounders were insignificant. The Jonckheere-Terpstra test is a rank-based non-parametric test that was used to assess for the presence of a significant trend in each variable from image reader scoring for increasing asthma severity. Receiver operating characteristic (ROC) curves were used to assess the predictive ability of the continuous predictors. Bland-Altman plots were used to assess inter-rater agreement. The limit of agreement was defined as twice the standard deviation of the difference between raters. Two sided *p*-values ≤ 0.05 were considered statistically significant. SAS version 9.4 (SAS System Inc., Cary, NC, USA) was used for statistical analysis.

Results

The ^{129}Xe MRI procedure was well tolerated and completed by all participants. There were no serious or severe adverse events (such as clinically significant oxygen desaturations or heart rate increases) as a result of ^{129}Xe MRI procedures in this study.

Study Population Demographics and Baseline Asthma Severity:

Thirty-seven children aged 6-17 (mean age = 11.6 ± 3.3 years-old) were imaged. 27% of subjects enrolled were non-white and 51% were female. There was no difference in age ($p=0.7$) or body mass index ($p=0.41$) between the groups. The mean FEV₁ values were not significantly different ($p=0.15$) between the severe asthma ($89.8 \pm 21.3\%$ predicted), mild/moderate asthma ($103.1 \pm 13.4\%$ predicted), and healthy control groups ($103.6 \pm 19.9\%$ predicted). There was a significant difference ($p=0.009$) between the mean FEV₁/FVC of the severe asthma (0.73 ± 0.091), mild/moderate asthma (0.83 ± 0.08), and healthy control groups (0.86 ± 0.075). After adjustment for multiple comparisons, there was significant difference between FEV₁/FVC of control and severe group ($p=0.008$), and the mild/moderate and severe group ($p=0.03$), but not the mild/moderate and control group ($p=0.68$).

All asthma subjects ($n=21$) had baseline clinical and asthma severity data obtained by EMR review. The baseline mean ACT scores for the severe and the mild/moderate asthma groups were 16.8 and 21.2 points, respectively, and were significantly different ($p=0.02$). Fifteen of 21 (71.4%) asthma subjects had at least one HCU event in the 12 months prior to MRI. Additional data are detailed in Table 1.

Image Analysis and Reader Scoring Results:

VDP was significantly different between the entire asthma cohort and the healthy controls ($p=0.002$). VDP between 3 groups was also significantly different ($p=0.002$, Figure 1). Similarly, reader scoring results showed a significant difference in number of defects/slice between the entire asthma cohort and the healthy controls ($p=0.0005$), and also among all 3 groups ($p<0.0001$, Figure 1). There was a significant relationship between VDP and number of defects/slice ($r=0.72$, $p<0.0001$) as shown in Figure 2. Analysis of the trend of individual scoring characteristics compared to asthma severity demonstrated a significant increase in number of defects/slice as severity of asthma increased (Table 2). Using Bland-Altman plots, we observed good inter-rater agreement for number, location, and size of lesion, but not shape of lesion. Figure 3 shows representative ^{129}Xe ventilation MR images of 4 subjects (3 asthma subjects, 1 healthy subject) which demonstrate the visual differences in semi-automated threshold defect detection, reader scoring, and the relationship to FEV_1 .

^{129}Xe MRI Correlation to Spirometry and Clinical Outcomes:

At baseline, VDP correlated with FEV_1 ($r=-0.35$, $p=0.04$) and FEV_1/FVC ($r=-0.41$, $p=0.01$). The number of defects/slice correlated with FEV_1/FVC ($r=-0.45$, $p=0.007$), although not with FEV_1 ($r=-0.16$, $p=0.35$). For baseline clinical outcomes, the number of defects/slice significantly correlated with HCU ($r=0.43$, $p=0.05$), rate of HCU ($r=0.48$, $p=0.03$), and rate of OCS use ($r=0.43$, $p=0.05$), but not with ACT score ($r=-0.33$, $p=0.16$). All baseline results are shown in Table 3.

Correlations between MRI and clinical indicators of asthma severity during the follow-up period are shown in Table 4. Twelve of 21 (57.1%) subjects with asthma did not have complete 12-month follow-up data as a result of the COVID-19 pandemic as

described in Methods (Mean number of months of follow up: 11 ± 1.36 months). The mean rate of OCS events was 0.16 ± 0.14 events/month for severe subjects and 0.03 ± 0.06 events/month for mild/moderate subjects during follow-up, which were statistically different ($p=0.03$). The mean rate of HCU was 0.13 ± 0.15 events/month for severe subjects and 0.01 ± 0.03 events/month for mild/moderate subjects, which were statistically different ($p=0.03$). During the follow-up period, the number of defects/slice was significantly correlated with the rate of OCS ($r=1.41$, $p=0.01$) and ACT score ($r=-1.2$, $p=0.02$).

ROC curves (Figure 4) demonstrated the number of defects/slice (area under curve, $AUC=0.83$) is more predictive of healthcare utilization than VDP ($AUC=0.73$). Similarly, number of defects/slice ($AUC=0.79$) slightly outperformed VDP ($AUC=0.75$) to predict asthma. Lastly, ROC curves showed that number of defects/slice is more predictive of severe asthma ($AUC=0.86$) than VDP ($AUC=0.80$).

Discussion

This is the first study to compare ^{129}Xe MRI in a cohort of children with asthma to age-matched healthy controls to examine the relationship between ^{129}Xe MRI, spirometry, and patient-centered outcomes. We demonstrated ^{129}Xe MRI can be used to quantify regional functional defects of the lungs in children with asthma, without clinically-significant adverse events.

Our study shows that ^{129}Xe MRI is correlated with increased asthma severity, specifically increased healthcare utilization and oral corticosteroid use. Even with relatively modest cohort numbers, ROC analysis demonstrates that VDP and image

scoring can predict increased asthma severity and healthcare utilization in a pediatric asthma cohort. ^{129}Xe MRI has many advantages as an imaging modality, including the non-ionizing, non-invasive testing, and the short and tolerable imaging process, which allow for longitudinal follow-up in children (37). ^{129}Xe MRI is routinely completed at our institution in children as young as 5 years-old (37-39).

Currently, there are no adequate predictive diagnostic tools for clinical severity in pediatric asthma that concurrently provide information about regional ventilation differences (21, 22, 31). Current tools are limited by patient-reported (or parent-reported) symptoms, the ability of the pediatric subject to complete the maneuver, and the effect of variability of medication adherence (5, 6). Eleven of 21 (52.4%) asthma subjects had not been able to complete spirometry at one time based on EMR review, and the average age was 10.5 ± 4.46 years-old at the time of the failed spirometry. ^{129}Xe MRI has the ability to visualize regional ventilation differences in children with asthma who are not able to perform spirometry and in those who have normal spirometry. Detection of subtle sub-clinical pathology by measuring regional lung function metrics may help clinicians determine treatment efficacy to prevent permanent airway remodeling.

While there have been significant advances in targeted biologic medications for children with severe asthma in the past decade, clinical measures of improvement and study endpoints for clinical trials mainly rely upon exacerbation rates for the 6-12 months following treatment. ^{129}Xe MRI may be able to offer an adjunctive option for predicting clinical response and measuring treatment efficacy in both research and clinical settings by providing regional lung function metrics. Although ^{129}Xe MRI is not

yet approved by the USFDA and is only available at select imaging research centers in tertiary or quaternary level care centers, the technology has expanded rapidly within the last few years and will become more readily available over time. Until it is more widely available, ^{129}Xe MRI will most likely be used in pediatric asthma subjects with clinically severe presentations who are likely to be referred to higher level medical centers.

In our study, we used both an established method for VDP calculation for semi-automated image analysis and a self-developed image scoring method, based on similar studies in ^3He MRI, to improve characterization of a clinically heterogeneous disorder that is expected to have subtle ventilation defects (31, 36, 40-43). Slight differences in analysis methods exist between imaging research groups and can affect the value of VDP in a given subject, though studies have shown that relative differences are preserved with consistent methods (44, 45). While VDP quantification offers the important advantage of full objectivity, reader scoring offers higher sensitivity at the expense of greater subjectivity and decreased repeatability. Future studies, particularly multicenter studies, will benefit from emerging international consensus on analysis methodology and may be able to utilize artificial-intelligence techniques to increase sensitivity of subtle defects like many of those observed here.

Future studies should not only enroll more subjects but also explore the nature of ventilation defects and their relationship to asthma severity, exacerbations, phenotypes, HCU, and treatment response. ^{129}Xe MRI can be paired with other existing diagnostic tools for pediatric asthma, such as lung CT and/or flexible bronchoscopy, to enhance the understanding of the relationship between ventilation defects, different phenotypes, and heterogeneous clinical presentations. ^{129}Xe MRI may also help localize areas of

pathology for treatments such as bronchial thermoplasty, as was recently shown in a single-site adult study (31).

The limitations of this study include the modest sample size. Also, since our institution is a quaternary-care center, the asthma cohort subjects tended to be more severe in clinical presentation, which may introduce a selection bias. We classified asthma severity based on EMR review, which does not account for the effects of adherence or clinical decisions. Poor adherence is a significant issue in pediatric asthma in the US, overall measuring 30-70% in previous studies (46-48). In future studies, it may be helpful to have a lead-in period prior to imaging to improve adherence to prescribed medications and follow-up. Lastly, the follow-up period for clinical exacerbations after imaging for some asthma subjects was shortened slightly to mitigate bias due to changes in HCU behavior related to the COVID-19 pandemic (49-51).

Hyperpolarized ^{129}Xe MRI of the lungs has potential to become a diagnostic tool in pediatric asthma to evaluate clinical severity and outcomes. Future studies are needed to fully understand how ^{129}Xe MRI may best be applied in clinical and translational research settings to predict asthma outcomes and treatment efficacy. This promising technique, which is non-invasive and non-ionizing, may be able to inform and enable clinicians to identify patients at higher risk for exacerbation. This will aid in development of personalized treatment plans and ultimately improve clinical outcomes in children with asthma.

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FIGURES LEGENDS

Figure 1. Box-and-whisker plots for ventilation defect percentage (left) and image reader scoring (right) by severity group with individual data points. Median and interquartile ranges are shown for VDP or number of defects per image slice. P-value shown is before adjusting for multiple group comparisons. After adjusting for multiple comparisons, there was a significant difference in VDP between the severe and healthy control groups ($p=0.003$), but not the mild/moderate and severe ($p=0.1$) and the mild/moderate and healthy control groups ($p=0.5$). After adjusting for multiple comparisons, the number of defects/slice was significantly different between the severe and healthy control groups ($p=0.005$), but not the mild/moderate and severe ($p=0.09$) and the mild/moderate and healthy control groups ($p=0.3$).

Figure 2. Spearman correlation demonstrating relationship between ventilation defect percentage and number of defects per image slice ($r=0.72$, $p<0.0001$).

Figure 3. [COLOR] Representative axial slices of ^{129}Xe ventilation MR images of 4 subjects (3 asthma subjects, 1 healthy control) which demonstrate visual differences between semi-automated threshold defect detection, reader scoring (both demarcated in red), and relationship to FEV₁. A) Severe II: Subject with severe asthma (NAEPP Step 6), abnormal lung function, and higher VDP and defects/slice. B) Severe I: Subject with severe asthma (NAEPP Step 6), normal lung function, and lower VDP and defects/slice compared to Severe II. C) Mild: Subject with moderate asthma (NAEPP Step 4), normal lung function, and lower VDP and defects/slice compared to severe subjects. D) Control: Healthy control subject without asthma, normal lung function, with similar VDP compared to the moderate subject, but lower defects/slice.

Figure 4. [COLOR] ROC curves with area under curve values to compare VDP (blue) and Number of Defects/Slice (red) are shown for healthcare utilization (left), severe asthma (middle) and asthma (right) prediction.

TABLES

Table 1. Baseline Study Population Characteristics ^a			
Demographics (n=37)			
Variable	Cohort	Mean ± SD or %	
Age, y	Severe Asthma (n=13)	12.1 ± 2.7	p=0.7
	Mild/Moderate Asthma (n=8)	11.9 ± 4.0	
	Healthy controls (n=16)	11.1 ± 3.5	
Sex (% Male)	All	49%	
	Severe Asthma	53%	
	Mild/Moderate Asthma	25%	
	Healthy controls	56%	
Race (% White)	All	73%	
	Severe Asthma	46%	
	Mild/Moderate Asthma	75%	
	Healthy controls	88%	
BMI (kg/m ²)	Severe Asthma	21.2 ± 5.3	p=0.41
	Mild/Moderate Asthma	18.4 ± 4.0	
	Healthy controls	19.9 ± 4.4	
Baseline Asthma Severity, Spirometry and Exacerbations (n=21) ^b			
Variable	Cohort	Mean ± SD or %	
FEV ₁ (% predicted) (n=37)	Severe Asthma	89.8 ± 21.3	p=0.15
	Mild/Moderate Asthma	103.1 ± 13.4	
	Healthy controls	103.6 ± 19.9	
FEV ₁ /FVC ratio (n=37)	Severe Asthma	0.73 ± 0.091	p=0.0009
	Mild/Moderate Asthma	0.83 ± 0.078	
	Healthy controls	0.86 ± 0.075	
Asthma Severity Group – NAEPP 2007	Step 1	n= 1 (4.8%)	
	Step 2	n= 4 (19 %)	
	Step 3	n= 2 (9.5%)	
	Step 4	n= 1 (4.8%)	
	Step 5	n= 1 (4.8%)	
	Step 6	n= 12 (57.1%)	
ACT Score	Severe Asthma	16.8 ± 3.3	p=0.02
	Mild/Moderate Asthma	21.2 ± 4.6	
Rate of OCS (Events/month)	Severe Asthma	0.2 ± 0.2	p=0.16
	Mild/Moderate Asthma	0.07 ± 0.07	
Rate of HCU (Events/month)	Severe Asthma	0.26 ± 0.36	p=0.22
	Mild/Moderate Asthma	0.09 ± 0.11	
Any HCU (Y)	Severe Asthma	10/13 (76.9%)	
	Mild/Moderate Asthma	5/8 (62.5%)	

- a. Demographic data were summarized using means and standard deviations for continuous measures and as proportions for discrete measures.
- b. Based upon electronic medical record review of 12 months leading up to MR imaging. N=21 unless otherwise specified.

Table 2. Image Reader Scoring				
	Severe Asthma	Mild/Moderate Asthma	Healthy Control	p-value for Trend^a
Variable	Median (IQR)	Median (IQR)	Median (IQR)	
Number Number of defects/slice	1.85 (0.6 – 3.4)	0.5 (0.1 – 1.6)	0.25 (0.08 – 0.5)	0.0004
Size # of defects ≥ 3 cm/slice # of defects < 3 cm/slice	1.0 (0.3 – 1.8) 0.95 (0.3 – 1.25)	0.2 (0 – 0.6) 0.14 (0.01 – 0.5)	0.05 (0 – 0.2) 0.09 (0 – 0.3)	<.0001 0.0019
Location # of peripheral defects/slice # of hilar defects/slice # of mixed defects/slice	1.1 (0.5 – 2.7) 0.05 (0 – 0.2) 0.35 (0.13 – 0.8)	0.46 (0.1 – 1.5) 0 (0 – 0) 0 (0 – 0.2)	0.25 (0.07-0.4) 0 (0 – 0) 0.03 (0 –0.1)	0.0006 0.0108 0.0014
Shape # of wedge defects/slice # of mixed defects/slice	0.85 (0.4 – 2.1) 0.95 (0.3 –1.3)	0.37 (0.05 – 1.1) 0.14 (0.01 – 0.5)	0.15 (0.02 – 0.3) 0.08 (0 – 0.3)	0.0015 0.0002

a. Jonckheere-Terpstra test for trend of each variable as severity increases from healthy control, to mild/moderate asthma, and to severe asthma.

Table 3. Correlation of VDP and Number of Defects/Slice to Baseline Indicators of Asthma Severity (n=21) ^a

		VDP		Number of defects/slice	
Variable	Mean $\pm$ SD (n=21)	Correlation Coefficient	p-value	Correlation Coefficient	p-value
NAEPP Step	4.6 $\pm$ 1.9	0.21	0.37	0.42	0.06
ACT score	18.6 $\pm$ 4.3	-0.09	0.72	-0.33	0.16
Any HCU (Y/N)	Yes: 15 (71.4%)	0.33	0.14	0.43	0.05
Rate of HCU (Events/month)	0.19 $\pm$ 0.3	0.27	0.23	0.48	0.03
Rate of OCS use (Events/month)	0.15 $\pm$ 0.2	0.20	0.39	0.43	0.05
FEV ₁ (% predicted)	98.3 $\pm$ 19.8	-0.35	0.04	-0.16	0.35
FEV ₁ /FVC ratio	0.81 $\pm$ 0.1	-0.41	0.01	-0.45	0.007

a. Based upon electronic medical record review of 12 months before imaging. N=21 unless otherwise specified. Results are reported as Spearman correlation with p-value.

ACT: Asthma control test, HCU: Healthcare utilization, OCS: oral corticosteroid

Table 4. Correlation of VDP and Number of Defects/Slice to Follow-Up Indicators of Asthma Severity (n=21) ^a

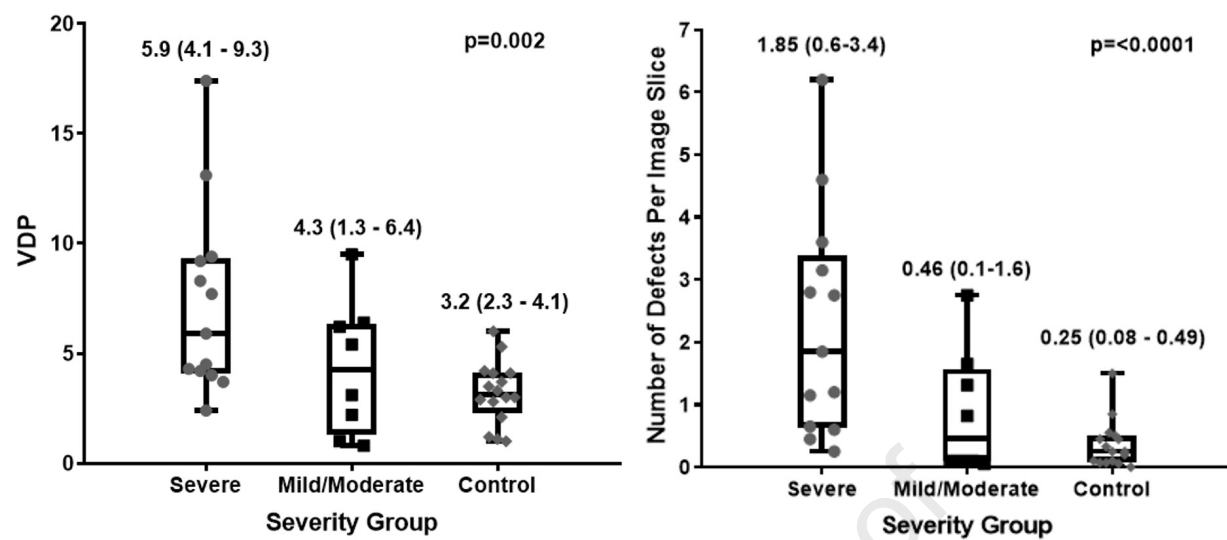
Variable	Mean $\pm$ SD (n=21)	VDP		Number of defects/slice	
		Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
ACT score	19.9 $\pm$ 3.9	-0.30 (-0.79, 0.19)	0.21	-1.20 (-2.20, -0.19)	0.02
Any HCU (Y/N)	Yes: 8 (38.1%)	1.15 (0.90, 1.45) ^b	0.26	1.79 (0.92, 3.50) ^b	0.09
Rate of HCU (Events/month) ^c	0.08 $\pm$ 3.9	1.08 (0.85, 1.38)	0.53	1.57 (0.90, 2.73)	0.11
Rate of OCS use (Events/month) ^c	0.11 $\pm$ 0.13	1.09 (0.95, 1.25)	0.23	1.41 (1.07, 1.84)	0.01
FEV ₁ (% predicted)	95.5 $\pm$ 15.8	-0.80 (-2.72, 1.12)	0.39	-1.19 (-5.74, 3.37)	0.59
FEV ₁ /FVC ratio	0.775 $\pm$ 0.11	-0.26 (-1.57, 1.04)	0.68	-0.91 (-3.94, 2.13)	0.54

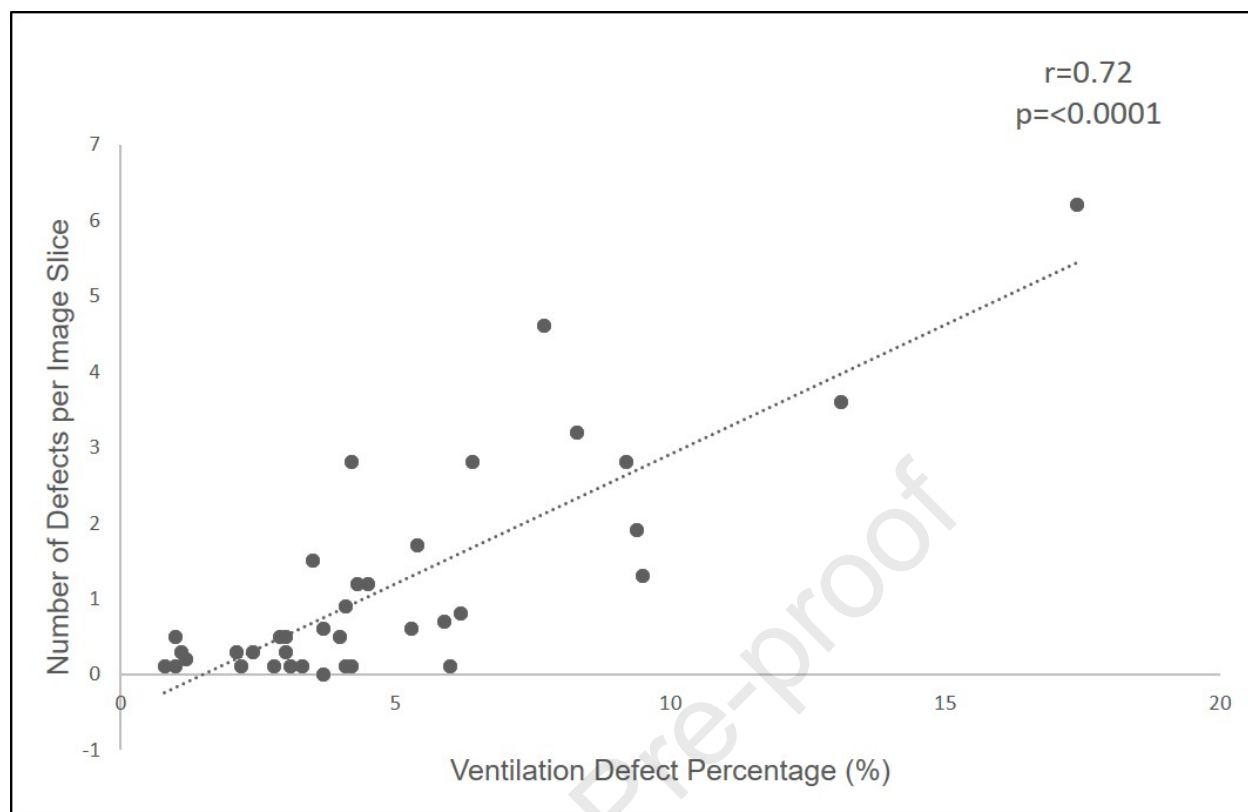
a. Based upon electronic medical record review of up to 12 months after imaging. The results are reported as estimates (with 95% CI and p-value) of coefficient or odds ratio or rate from linear regression or logistic regression or negative-binomial regression as appropriate.

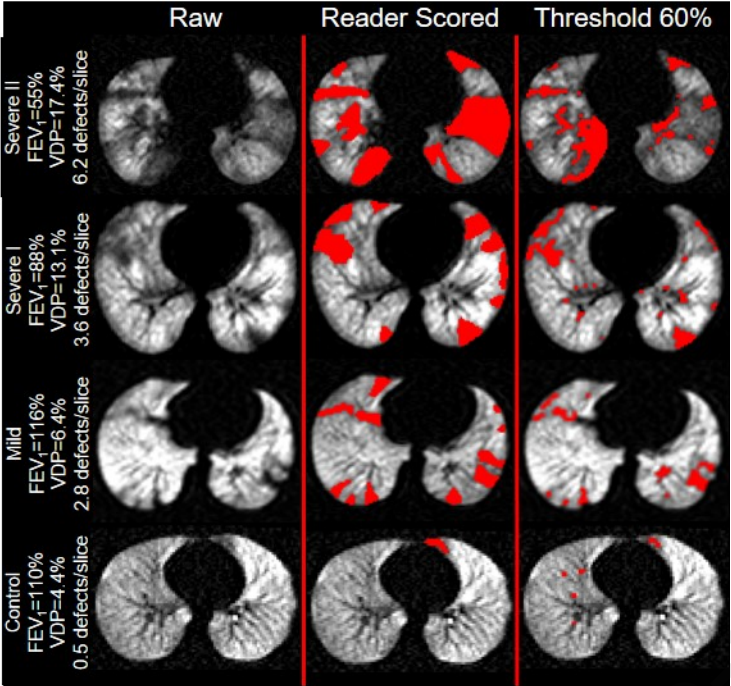
b. Odds ratio estimate

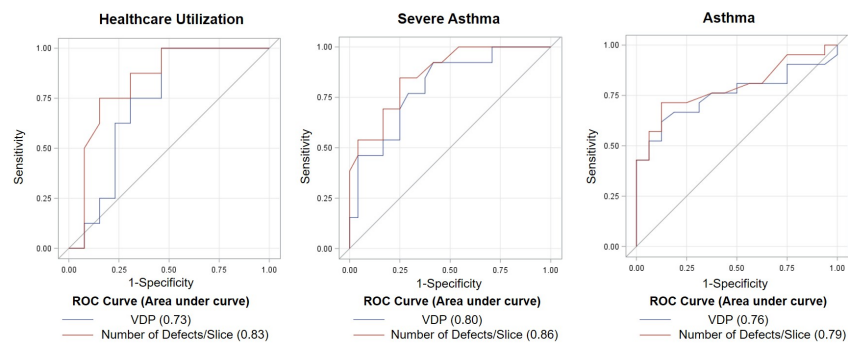
c. Rate estimate

ACT: Asthma control test, HCU: Healthcare utilization, OCS: oral corticosteroid, 95% CI: 95% confidence interval









Online Repository

I. Detailed Description of Study Visits

Screening Phone Call

Prior to the study visit, the study coordinator reached out to the subject's parent or guardian via telephone to explain the study aims and procedures in detail. During this screening phone call, the study coordinator reviewed the 'Phone MRI Safety Review Form' to confirm that the subject passes MRI safety screening (i.e. no metal devices in the subject's body). The subject's height and weight were also confirmed with the parent or guardian to estimate hyperpolarized xenon dose.

Day of Study Visit

On the day of the study visit, the coordinator reviewed the informed consent thoroughly with the subject and his or her parent or guardian. Informed consent was signed before any study procedure was performed and assent was obtained from subjects ≥ 11 years-old. The coordinator and an MRI technologist confirmed the answers on the 'Phone MRI Safety Review Form'. Other parameters measured on the day of the study visit, prior to imaging were: weight and vital signs (blood pressure, heart rate, respiratory rate and oxygen saturation). A pregnancy test was done for all female subjects of reproductive age who have had menarche. The study coordinator reviewed demographics, medical history, medication lists and inclusion/exclusion criteria with the subject's parent or guardian. A focused physical examination was performed for all subjects by one of the study medical personnel (registered nurse or physician).

Follow-Up Call

One day after the study visit, the study coordinator completed a follow-up phone call to the subject's parent or guardian. During this call, the coordinator asked how the patient was feeling, if he/she had experienced any adverse events since the MRI, and if any adverse events (if applicable) from the MRI visit were unresolved.

II. ^1H Proton MRI

At the start of the imaging protocol, structural lung images were acquired via a radial 3D ^1H ultrashort echo-time (UTE), stack of stars, MRI sequence. Images were acquired with the following parameters: repetition time 4.7ms, echo time 0.2 ms, field of view 300x300 to 400x400 mm², voxel size 1.39x1.39x4.00 mm³. An echo navigator was positioned on the lung-liver interface to gate the acquisition and capture lung signal at functional residual capacity. ^1H UTE images were used for semi-automated analysis.