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Original Article

A two-center analysis of hyperpolarized ^{129}Xe lung MRI in stable pediatric cystic fibrosis: Potential as a biomarker for multi-site trials

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ABSTRACT

Background: The ventilation defect percent (VDP), measured from hyperpolarized (HP) ^{129}Xe magnetic resonance imaging (MRI), is sensitive to functional changes in cystic fibrosis (CF) lung disease. The purpose of this study was to measure and compare VDP from HP ^{129}Xe MRI acquired at two institutions in stable pediatric CF subjects with preserved lung function.

Methods: This retrospective analysis included 26 participants from two institutions (18 CF, 8 healthy, age range 10–17). Pulmonary function tests, N_2 multiple breath washout (to measure lung clearance index, LCI), and HP ^{129}Xe MRI were performed. VDP measurements were compared between two trained analysts using mean-anchored linear binning. Correlations were investigated for VDP compared to the forced expiratory volume in one second (FEV_1) and LCI.

Results: VDP measurements agreed for the two analysts with an intraclass correlation coefficient of 0.99. In the combined dataset, VDP measured by Analyst 1 was 5.96 ± 1.82% and 15.96 ± 6.76% for the healthy and CF groups, respectively ($p = .0004$). Analyst 2 showed similar differences between healthy and CF ($p = .0003$). VDP measured by either analyst was shown to correlate with FEV_1 ($R^2 = 0.33$, $p = .003$; and $R^2 = 0.26$, $p = .009$ for Analysts 1 and 2, respectively) and LCI ($R^2 = 0.76$, $p < .0001$; and $R^2 = 0.77$, $p < .0001$ for Analysts 1 and 2, respectively).

Conclusion: HP ^{129}Xe MRI provides a robust measurement of ventilation heterogeneity in stable pediatric CF subjects at two sites. Since measurements performed at two sites yielded similar VDP values with near-identical values between different analysts, implementation of the technique in multi-center trials in CF appears feasible.

1. Introduction

Hyperpolarized (HP) ^{3}He or ^{129}Xe magnetic resonance imaging (MRI) provides a sensitive measure of ventilation heterogeneity in pediatric cystic fibrosis (CF) patients with preserved lung function [1,2]. HP gas MRI is typically performed during a breath-hold following inhalation of a dose of HP ^{3}He or ^{129}Xe, and the images reflect the distribution of the inhaled gas inside the lungs. In obstructive lung diseases such as CF, the HP gas does not fully equilibrate with the whole lung in a single breath, resulting in a heterogenous image with signal voids that represent unventilated or poorly ventilated regions of the lung. Early HP gas MRI studies in CF have assessed the ventilation distribution using reader scoring systems [3] and counting the ventilation defects [4]. In recent years, HP gas MRI studies in CF have objectively quantified the spatial distribution of ventilation using a ventilation defect percent, or VDP [2,5], which is defined as the fraction of unventilated lung (i.e., the ventilation defect volume divided by the total lung volume, represented as a percentage).

While previous HP gas MRI studies in CF have used both ^{3}He [6–8] and ^{129}Xe [2,5,9], future studies will likely focus on using HP ^{129}Xe due to the lower cost and greater availability of the gas. HP ^{3}He and ^{129}Xe VDP measurements have been successfully validated in other obstructive lung diseases, such as chronic obstructive pulmonary disease, with a slightly greater VDP expected from HP ^{129}Xe MRI due to the greater density and lower diffusivity of the inhaled gas compared to ^{3}He [10]. VDP is potentially more sensitive for detecting functional changes in the lungs compared to pulmonary function test (PFT)

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indices, such as the forced expiratory volume in one second (FEV_1) [2]. VDP has been shown to be reproducible in stable CF lung disease [8], and sensitive to changes in ventilation distribution that may not be detectable using FEV_1 alone [7]. One study in pediatric CF reported an increased VDP in CF patients compared to healthy controls, whereas FEV_1 did not differentiate between both groups [2]. In addition, VDP is strongly correlated with multiple breath washout (MBW) measurements of the lung clearance index (LCI), which is a measure of ventilation heterogeneity [5]. Therefore, VDP has the potential to be used as an outcome measure for the management of CF lung disease and testing novel therapeutics, such as CF transmembrane conductance regulator (CFTR) modulators [6].

Before HP gas measures can be adopted clinically, multi-center prospective clinical trials will need to be performed, which will require a harmonized VDP analysis approach. Therefore, standardized procedures will be required for consistent acquisition and analysis between centers, which will be especially important for sites that may be using different MRI platforms, different RF coil hardware, and different HP ^{129}Xe dosing strategies. As a preliminary step in the pathway to clinical translation, we performed a retrospective analysis of HP ^{129}Xe images from similar stable pediatric CF subjects obtained at two different institutions using slightly different MRI systems to assess the following: (i) the agreement between VDP measurements performed by two trained analysts using the same software, and (ii) the correlation between VDP and PFT measurements (i.e., FEV_1 and LCI).

2. Methods

2.1. Subjects

This study was a retrospective analysis that included previously reported image data acquired at the Hospital for Sick Children (Site #1) in Toronto, Ontario, Canada [5] and Cincinnati Children's Hospital Medical Center (Site #2) in Cincinnati, OH, USA [2]. The study at Site #1 was regulated by Health Canada and approved by the Hospital for Sick Children Research Ethics Board (clinicaltrials.gov registry number NCT02740868). The study at Site #2 was regulated by an FDA investigational new drug approval (IND 123,577) and approved by the Cincinnati Children's Institutional Review Board (clinicaltrials.gov registry number NCT02272049). Table 1 summarizes the subject demographics for 16 pediatric participants at Site #1 and 10 pediatric participants at Site #2, all between the ages of 10 and 17. The combined dataset included 18 well-controlled stable CF participants and 8 age-matched healthy controls ($p = .73$). Well-controlled stable CF was defined as having no changes in respiratory symptoms or medication for four weeks (Site #1) or one week (Site #2) prior to participation in the study.

2.2. Site #1 data acquisition

The study at Site #1 performed pulmonary function tests (PFTs), nitrogen multiple breath washout (N_2 MBW) and HP ^{129}Xe MRI in a single study visit. Spirometry and plethysmography were performed (Vmax, VIASYS CareFusion, San Diego, CA, USA) by qualified research team members according to ATS guidelines [11]. N_2 MBW was performed to determine LCI (Exhalyzer D, EcoMedics, Duernten, Switzerland) by qualified research team members, according to ERS/ATS standards [12]. LCI was defined as the cumulative expired volume required to achieve 1/40th of the initial N_2 concentration divided by the functional residual capacity (FRC).

HP ^{129}Xe MRI was performed in the coronal plane at 1.5 T (HDx, GE Healthcare, Waukesha, WI) using a flexible wrap-around quadrature transmit/receive RF coil tuned to the ^{129}Xe resonance frequency (Clinical MR Solutions, Brookfield, WI, USA). Isotopically enriched ^{129}Xe (83%) was polarized to approximately 15% (Model 9800, Polarean, Durham, NC, USA) and dispensed into a 1 L Tedlar bag (Jensen Inert Products, Coral Springs, FL, USA). The HP ^{129}Xe dose was set to 10% of total lung capacity (TLC), as measured using plethysmography, and balanced to 1 L with medical grade N_2. Throughout the imaging session, the subject's oxygen saturation and heart rate were monitored.

Following inhalation of the dose bag from FRC, HP ^{129}Xe images were acquired in a 16 s breath-hold using a fast spoiled gradient recalled echo (GRE) sequence (see the online supplement for a summary of all imaging parameters used in both studies). Most participants had two repeated HP ^{129}Xe scans within a few minutes of each other. Following HP ^{129}Xe imaging, the ^{129}Xe vest coil was exchanged for an 8-channel torso array coil (GEHC) and conventional ^{1}H lung images were acquired. For ^{1}H imaging, subjects breathed in a 1 L dose bag of N_2 from FRC and GRE images were acquired in a 13 s breath-hold.

Table 1
Subject demographics and pulmonary function tests for all participants included in the retrospective study.

	Subject	Age	Sex	Height (cm)	Weight (kg)	FEV_1 (% pred.)	LCI	Genotype
Site #1 Healthy	1	10	F	146	40.5	84	6.17	–
	2	13	F	152	41.3	96	7.17	–
	3	11	M	145	32.6	94	6.74	–
	4	17	M	168	60.8	95	6.06	–
	5	11	F	132	42.6	137	7.11	–
	6	14	M	163	52.9	129	–	–
Site #1 CF	7	17	M	170	55.3	74	16.87	DeltaF508/DeltaF508
	8	10	F	143	30.6	109	6.83	DeltaF508/DeltaF508
	9	10	F	140	31.2	86	9.10	DeltaF508/DeltaF508
	10	11	F	141	30.4	81	11.71	DeltaF508, Duplications of exons 7–11
	11	14	M	175	57.0	71	11.98	G480S/A559T
	12	11	F	144	31.4	61	15.35	C.1653_1655delCTT/c.1837 T > G
	13	16	F	152	37.4	78	15.98	DeltaF508/DeltaF508
	14	16	F	148	43.5	83	10.88	W1282X/1282X
	15	14	F	145	38.5	96	9.08	W1282X/1282X
	16	11	M	156	38.2	99	9.56	DeltaF508/DeltaF508
Site #2 Healthy	17	14	M	177	64.8	106	–	–
	18	12	M	141	34.8	103	–	–
Site #2 CF	19	14	M	167	54.4	97	11.28	DeltaF508/DeltaF508
	20	12	F	162	43.6	77	15.28	DeltaF508/DeltaF508
	21	13	F	161	48.9	96	8.49	G551D, F508
	22	14	F	156	51.2	106	6.73	F508, L206 W
	23	16	M	179	65.5	120	9.81	DeltaF508/DeltaF508
	24	11	M	142	34.5	102	–	F508, G178R
	25	15	F	159	43.7	72	–	DeltaF508/DeltaF508
	26	11	F	147	34.3	86	11.01	DeltaF508/DeltaF508

2.3. Site #2 data acquisition

The study at Site #2 used an approach that was similar to the Site #1 study, with some important differences. PFTs, N_2 MBW and HP ^{129}Xe MRI were not necessarily performed in a single study visit. Same-day spirometry was performed (Koko, nSpire, Longmont, CO) if clinical PFTs had not been performed in the last six months. Plethysmography was not performed, but instead the participant's height was used to estimate TLC for HP ^{129}Xe dosing. Unlike the Site #1 study, where dose bags used a fixed 1 L volume, the Site #2 study used dose bags that were filled to 1/6th of the participant's TLC. Dose bags were either 100% HP ^{129}Xe, or a mixture of 50% HP ^{129}Xe/ 50% N_2, depending on the gas polarization (described below). N_2 MBW was performed on the same day if possible, or up to 34 weeks after the MRI study visit (Exhalyzer D, EcoMedics, Duernten, Switzerland).

HP ^{129}Xe MRI was performed in the axial plane at 3 T (Philips Achieva, Best, Netherlands) using a home-built ^{129}Xe saddle RF coil. ^{129}Xe was polarized using either a commercially-built system (Polarean, Durham, NC, USA) or a home-built polarizer. Dose bags from the commercially-built polarizer were filled with 100% ^{129}Xe, while dose bags from the home-built system were diluted with 50% N_2. Either case resulted in a similar signal-to-noise ratio (SNR) since the home-built system provided up to double the polarization of the commercially-built system (~30%). Similar to the Site #1 study, HP ^{129}Xe and conventional ^{1}H acquisitions used coached inhalations from FRC and breath-holds of up to 16 s. Conventional ^{1}H imaging used the integrated ^{1}H body coil without moving the participant or ^{129}Xe coil. The ^{1}H and HP ^{129}Xe image acquisitions at Site #2 both used a GRE pulse sequence, and the parameters are shown in the online supplement.

2.4. Data analysis

VDP was measured by two trained individuals using the mean-anchored linear binning technique described by Thomen et al. [2]. Both analysts independently processed the images from all 26 participants. Analyst 1 had one year of experience in lung image analysis, while Analyst 2 had seven years of experience. The ^{1}H images were segmented to create a lung mask using seeded region-growing in 3D Slicer (https://www.slicer.org), and then registered to HP ^{129}Xe images using a landmark-based approach with affine transformations [1]. The region-growing algorithm excluded large blood vessels from the thoracic cavity mask, but an explicit vesselness filter was not implemented to remove smaller blood vessels [13,14]. If there were any registration errors, due to differences in lung inflation between the ^{1}H and HP ^{129}Xe acquisitions, the analyst performed manual corrections to the thoracic cavity mask.

After the preliminary segmentation and registration steps, VDP was measured in Matlab (Mathworks, Natick, MA, USA). A bias field correction was used to account for RF coil inhomogeneities, where each HP ^{129}Xe voxel was divided by the mean lung signal value in each dimension (anterior-posterior, left-right, apex-base). The HP ^{129}Xe image volume was divided by the mean signal value inside the lung mask, and voxels with a signal <60% of the mean value were considered part of the defect region. The VDP threshold was set based on a study that included a similar age-matched population of healthy children and pediatric CF patients, where a 60% signal threshold was shown to provide the maximum difference between VDP values measured in healthy and diseased lungs [2]. Before calculating the final VDP, a median filter (3×3 kernel) was applied to the defect mask obtained from linear binning [15].

The final VDP was calculated as the total volume of unventilated lung obtained from the ^{129}Xe images divided by the total lung volume obtained from the ^{1}H image masks. VDP was compared between analysts using a Bland-Altman analysis in GraphPad Prism (Graphpad Software, La Jolla, CA, USA). The inter-analyst reliability of VDP measurements was assessed by calculating the intraclass correlation coefficient (ICC) in Matlab. HP ^{129}Xe images with a center slice SNR below 8.5 were excluded from the Bland-Altman and correlation analyses. The SNR threshold of 8.5 was determined by the trained analysts, based on the ability to reliably co-register the ^{1}H and ^{129}Xe images in a given subject. VDP was compared between groups using a Mann-Whitney test, with $p < .05$ being considered significant. VDP was also correlated with FEV_1 and LCI using a linear regression analysis in GraphPad Prism. Where possible, LCI was retrospectively analyzed by the MBW over-read center at Site #1. For eight subjects at Site #2, the MBW raw data was lost and the LCI could not be re-processed. In those cases, the MBW raw data was not over-read and the LCI value provided by Site #2 was used.

3. Results

Fig. 1 shows a comparison of segmented ventilation and defect maps obtained from HP ^{129}Xe MRI performed by both analysts in two representative CF patients at Site #1 and Site #2, respectively. Both analysts identified qualitatively similar thoracic cavity masks, as well as similar segmented masks and VDP results. The HP ^{129}Xe images included in this study (SNR > 8.5) had a mean SNR of 15.1 ± 3.8 and 18.2 ± 4.7 for Sites 1 and 2, respectively ($p = .12$). Table 2 summarizes the VDP results for the healthy and CF patient cohorts, separated by institution and analyst. Fig. 2(a) and (b) show the VDP results as box and whisker plots separated by institution and also as a combined dataset. VDP was significantly different between the healthy and CF groups for the Site #1 data and also for the combined dataset ($p < .05$ for either analyst). There were not enough healthy participants at Site #2 to reach a significant difference for that subset. The CF cohorts from the two sites had VDP values that were not significantly different from one another ($p = .44$ and $p = .46$ for Analysts 1 and 2, respectively).

Fig. 2(c)shows a Bland-Altman analysis for VDP measurements performed by the two analysts. The mean bias (± standard deviation) in VDP between analysts was insignificant (0.14 ± 1.46), and the inter-analyst ICC was 0.99 ($p = 0$). The average absolute difference in VDP between Site #1 and Site #2 was 3.7 and 3.0 percentage points for Analysts 1 and 2, respectively. VDP measurements obtained by the two analysts were strongly correlated with one another ($R^2 = 0.96$, $p < .0001$). Fig. 3(a) and (b) show a correlation analysis for FEV_1 compared to VDP measured by Analyst 1 and Analyst 2, respectively. For both analysts, there was a weak to moderate negative correlation between VDP and FEV_1, when either the Site #1 data or the combined dataset were considered. Fig. 3(c) and (d) show the relationship between VDP and LCI for both analysts, confirming the expected strong positive correlations; however, there was a significant correlation between VDP and LCI only when either the Site #1 data or the combined dataset were considered, underlining the value added by combining data from the two sites.

4. Discussion

To our knowledge, this study is the first to compare VDP measurements obtained from HP ^{129}Xe MRI performed in stable pediatric CF subjects at two institutions. In a combined ^{129}Xe image dataset consisting of 28 pediatric participants (8 healthy, 18 CF), good inter-observer agreement was demonstrated for VDP values measured by two trained analysts, and the VDP results were similar for the two populations of mild pediatric CF lung disease (Table 2). VDP was significantly different between the healthy and CF groups in the combined dataset, while data from the individual sites may lack statistical power. Therefore, there is strong potential for the use of HP ^{129}Xe MRI in future multi-center trials.

This study showed the expected correlations with physiological parameters; VDP showed a weak to moderate correlation with FEV_1 and a strong correlation with LCI. Although stronger correlations have been previously reported between VDP and LCI in stable pediatric CF subjects

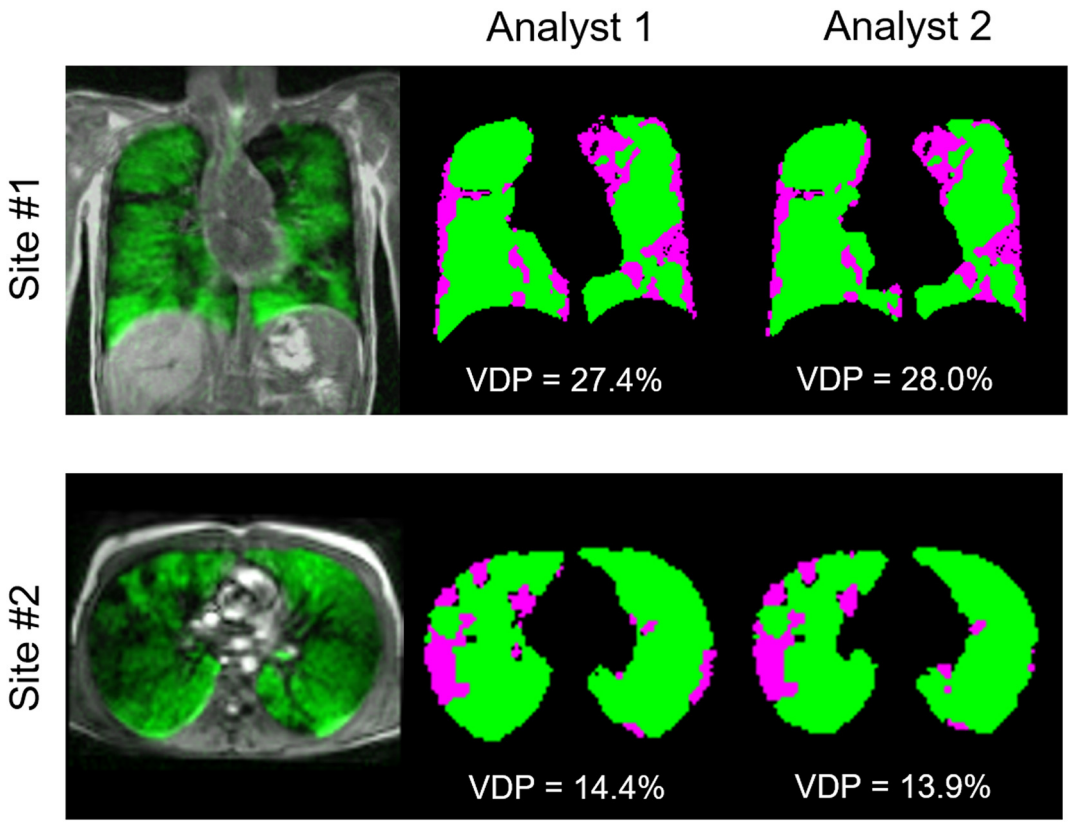

Fig. 1. Comparison of segmented ventilation and defect maps obtained from two representative CF patients at Site #1 (top) and Site #2 (bottom). The leftmost images show an overlay of the center slice HP ^{129}Xe image in green, with the ^{1}H image in greyscale. VDP results and segmented maps are shown for both trained analysts, where ventilated areas are shown in green and defect areas are shown in purple.

Table 2
Comparison of subject demographics, pulmonary function tests, and VDP results for all participants included in the retrospective study. Results are shown separately for each institution and also as a combined dataset.

	Site #1			Site #2			Combined		
	Healthy	CF	p Value	Healthy	CF	p Value	Healthy	CF	p Value
n	6	10	–	2	8	–	8	18	–
Sex (males)	3	3	–	2	3	–	5	6	–
Age (mean ± SD)	12.7 ± 2.6	13.0 ± 2.7	0.8945	13.0 ± 1.4	13.3 ± 1.8	1	12.7 ± 2.3	13.1 ± 2.3	0.7299
FEV_1 (% pred. ± SD)	105.8 ± 21.6	83.8 ± 14.3	0.0593	104.5 ± 2.1	94.5 ± 15.7	0.2889	105.5 ± 18.3	85.6 ± 15.5	0.0636
LCI (± SD)	6.68 ± 0.47	11.52 ± 3.12	0.0017	*	10.39 ± 2.77	*	7.05 ± 0.99	11.10 ± 2.95	0.0012
Analyst 1 VDP (% ± SD)	6.55 ± 0.74	16.38 ± 6.15	0.0012	1.80**	13.72 ± 7.25	**	5.96 ± 1.82	15.96 ± 6.76	0.0004
Analyst 2 VDP (% ± SD)	5.76 ± 2.05	16.56 ± 6.90	0.0012	2.81**	13.47 ± 6.58	**	5.39 ± 2.17	15.48 ± 6.79	0.0003

* LCI was not available for the healthy participants from Site #2.
** Only one healthy individual at Site #2 had HP ^{129}Xe images that were acceptable for analysis (SNR > 8.5).

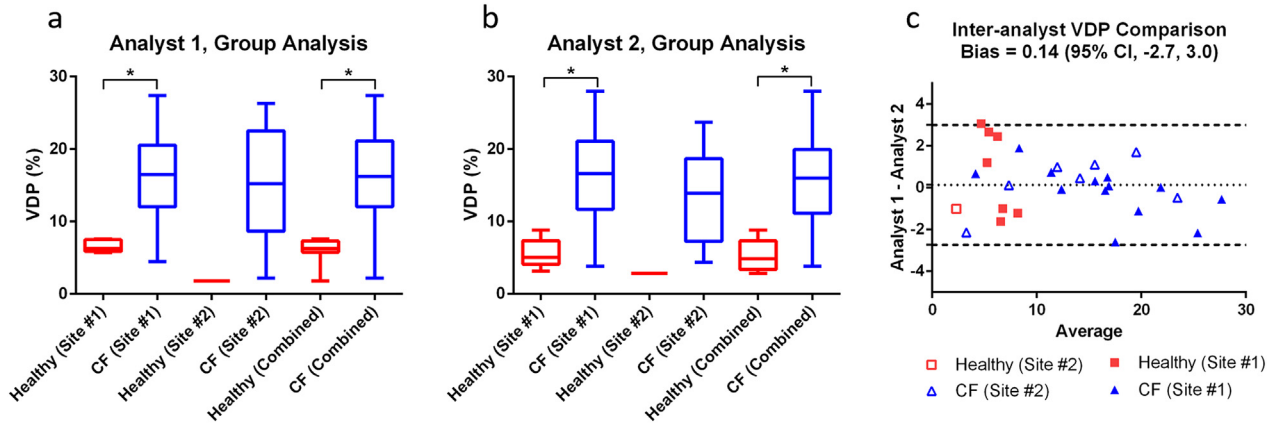

Fig. 2. Box and whisker plots showing the VDP measured by (a) Analyst 1 and (b) Analyst 2 for healthy and CF cohorts. VDP results are shown separately for each institution and also as a combined cohort. (c) Bland-Altman analysis showing the inter-analyst agreement for all VDP measurements in the combined dataset.

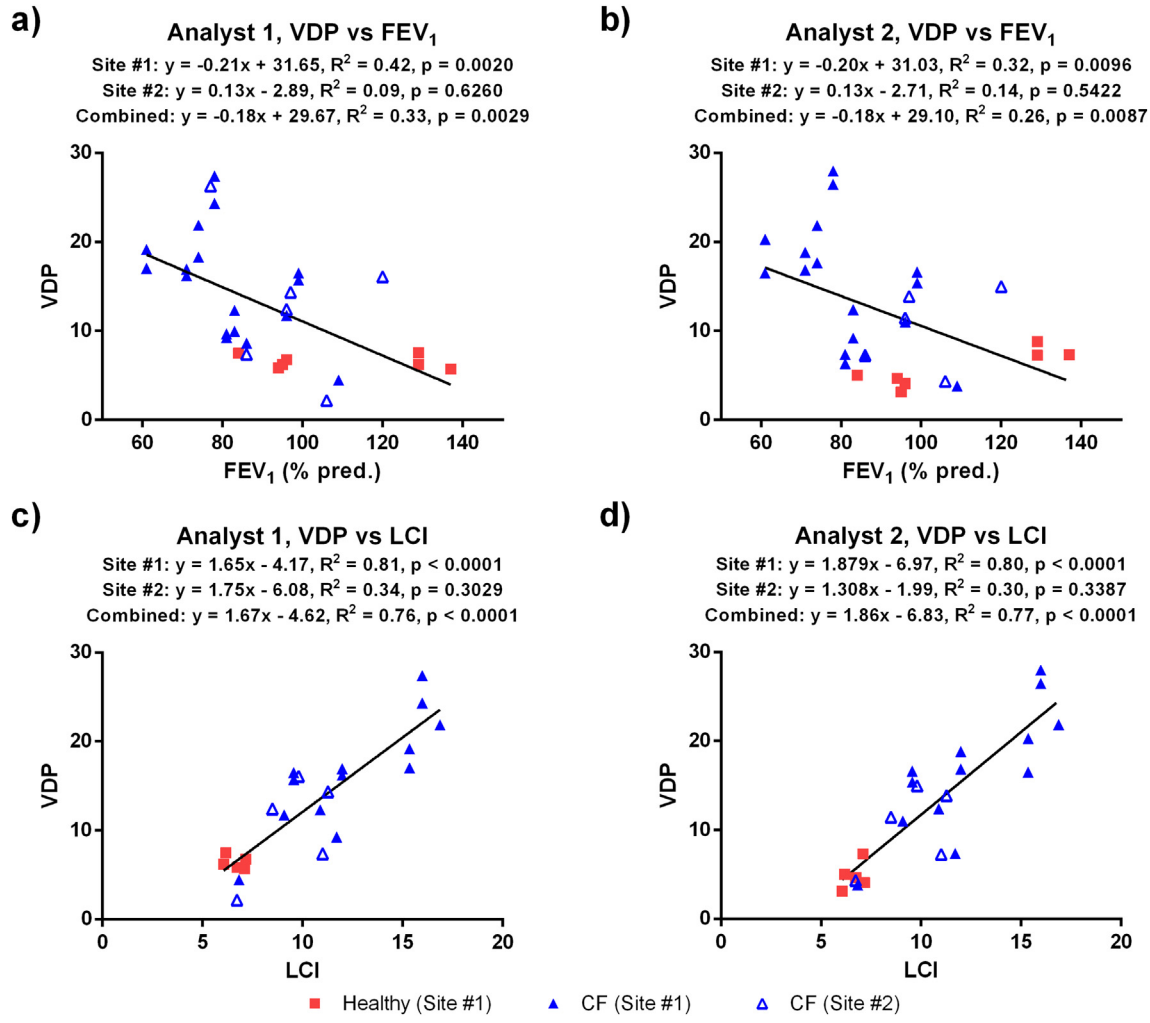

Fig. 3. (a,b) Correlation between VDP and FEV_1 for both analysts. (c,d) Correlation between VDP and LCI for both analysts. For each plot (a-d), the solid line represents the correlation for the combined dataset, while the plot title includes the separate correlations for each site.

[5], the slightly reduced correlations in the present study likely reflect the variability introduced by the inclusion of multi-center data combined with differences in the data acquisition. Although there was good agreement in VDP between analysts, some small differences in VDP results can likely be attributed to the $^{1}H/^{129}Xe$ registration and thoracic cavity segmentation. While the VDP calculation was largely automated, the initial segmentation and registration steps required some manual input and adjustments. As the VDP increased, the analysts noted that it became more difficult to find matching landmarks between ^{1}H and HP ^{129}Xe images, especially when the defects were large and encompassed an entire lung lobe. To avoid potential misregistration issues, future work will explore the simultaneous acquisition of ^{1}H and HP ^{129}Xe lung images in the same breath-hold [6,16]. Without the need to register the ^{1}H and HP ^{129}Xe images, the VDP analysis could potentially be fully automated.

There are a few limitations in this study, which stem from the retrospective nature of the analysis. That is, images were acquired at two institutions that used different hardware, magnetic field strengths, scanner vendors, and RF coil designs. In addition, the two sites used similar pulse sequences, but with slightly different acquisition parameters. Even though the two sites had different configurations, both were able to acquire good quality HP ^{129}Xe images, and the VDP appears to be a robust measure of ventilation heterogeneity in these healthy children and stable pediatric CF subjects. The SNR was expected to be slightly higher at 3 T compared to 1.5 T [17]; however, the SNR difference in this retrospective study was too small to be statistically significant. Therefore, SNR was not expected to significantly influence the VDP. The original studies at both institutions only acquired low resolution ^{1}H images to facilitate VDP calculation; however, future studies will also acquire high resolution ^{1}H images for morphological scoring. Previous studies have shown that ^{1}H MRI morphological scores are able to detect structural abnormalities in CF [18,19]. In addition, ^{1}H morphological scores are correlated with LCI and are sensitive to CF treatment response [20].

Another limitation of this study was the difference in dosing strategies used by the two institutions. Since the Site #1 cohorts used a 1 L bag volume, the total lung volume for imaging breath-holds (i.e., FRC + 1 L) was likely close to TLC in some of the younger pediatric subjects. On the other hand, the Site #2 cohorts used a smaller bag volume (i.e., 1/6th of TLC), which would have been closer to a comfortable inspiratory tidal volume. It has been shown that the inhaled dose volume affects VDP results, with larger inspiratory volumes leading to a reduced VDP [21]. A larger inhaled volume can fill areas of the lung that would otherwise be obstructed at smaller volumes; however, it has also been shown that both dosing approaches lead to similar correlations between VDP and LCI [21]. Despite the different dosing strategies used at the two sites, VDP appears to provide a robust measure of ventilation heterogeneity. This result might be explained by the use of mean-anchored linear binning to calculate VDP, which uses a fixed signal threshold that includes some partially ventilated areas of the lung. Since Site #1 used a larger dose volume, it is possible that some partially ventilated areas of the lung might have appeared as defect had the dosing used a smaller

volume. Nevertheless, the inclusion of partially ventilated regions in mean-anchored linear binning results in a similar VDP for the two CF populations. Future work will continue to investigate the sensitivity of other VDP calculation methods in multi-center trials, such as k-means [22,23], spatial fuzzy c-means clustering [24] or variations of the linear binning approach [25,26].

HP ^{129}Xe MRI is a relatively new and sensitive technique, and although more experience is required to fully implement in multi-center clinical trials [27,28], this study presents a step forward in assessing multi-site variability in methods and endpoints. This comparative work demonstrates strong agreement using HP ^{129}Xe MRI between two pediatric CF settings and we conclude that multi-center clinical trials using this approach are feasible. Future multi-center studies will focus on standardizing the image acquisition protocols and parameters. A recent multi-center study has shown that standardizing ^{1}H-based MRI is feasible in pediatric CF [29]. Based on the somewhat limited availability of HP ^{129}Xe MRI technology at the current time, it is likely that ^{1}H-based imaging techniques will see more widespread clinical adoption; however, HP ^{129}Xe MRI is anticipated to be used in specialized centers upon regulatory approval. HP ^{129}Xe MRI will likely play a role in providing outcome measures for interventional trials involving CFTR modulators, and may also play a role in future clinical management via precision medicine. Since HP ^{129}Xe MRI can potentially detect CF lung disease before traditional PFTs [2], its sensitivity may allow for interventional trials with fewer subject numbers than previous studies using FEV_1 or LCI as outcome measures [30].

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcf.2019.03.005.

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