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Sensitive Structural and Functional Measurements and 1-Year Pulmonary Outcomes in Pediatric Cystic Fibrosis

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Abstract

Background: Two functional measurements (multiple breath washout [MBW] and hyperpolarized ^{129}Xe ventilation magnetic resonance imaging [^{129}Xe MRI]) have been shown to be more sensitive to cystic fibrosis (CF) lung obstruction than traditional spirometry. However, functional techniques may be sensitive to different underlying structural abnormalities. The purpose of this study was to determine relationships between these functional markers, their pathophysiology, and 1-year clinical outcomes.

Methods: Spirometry, MBW, ^{129}Xe MRI, and ultrashort echo-time (UTE) MRI were obtained in a same-day assessment of 27 pediatric CF patients (ages 11.5±5.0) who had not begun CFTR modulator therapies. UTE MRI was scored for structural abnormalities and functional metrics obtained via spirometry, MBW and ^{129}Xe MRI. 1-year outcomes (FEV_1 and pulmonary

exacerbations), during which ≈50% initiated modulator therapy, were obtained from the electronic medical record.

Results: MBW, ^{129}Xe MRI, and UTE MRI detected clinically significant disease in more subjects (>78%) compared to spirometry (<30%). UTE MRI suggests increased odds of bronchial changes when mucus plugging is present in the same lobe. MBW and ^{129}Xe MRI correlated best with mucus plugging, while spirometry correlated best with consolidations. Bronchial abnormalities were associated with future pulmonary exacerbations.

Conclusions: MBW, ^{129}Xe MRI, and UTE MRI are more sensitive for detection of pediatric CF lung disease when compared to spirometry. MBW and ^{129}Xe MRI correlated with structural abnormalities which occur in early CF disease, suggesting MBW and ^{129}Xe MRI are valuable tools in mild CF lung disease that can guide clinical decision making.

Keywords

Spirometry; Multiple Breath Washout; Xenon; MRI; Structure; Function

Introduction:

Cystic Fibrosis (CF) results in multiple morphological lung abnormalities on computed tomography (CT) examination that are identified as mucus plugging, bronchial wall thickening, bronchiectasis, ground glass opacities, consolidations, and cysts. Significant intra- and inter-subject heterogeneities in abnormalities exist with variability in severity and lobar distribution [1]. The structural abnormalities eventually result in a loss of clinical lung function, which is periodically monitored to follow disease progression and treatment response.

Previous studies have shown the use of cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies increased lung function and reduced bronchial wall thickening and mucus plugging [2]. Recently, a triple-combination CFTR) modulator therapy has been shown to be a highly effective treatment, with a greater than 10% improvement in lung function for any patient with a single *F508del* mutation (~90% of all CF patients) [3]. With highly-effective therapies becoming more widely used, we anticipate a larger fraction of subjects will likely exhibit milder lung disease, both structurally and functionally. Thus, sensitive measures of lung disease progression and outcomes is a growing necessity.

Chest CT is the imaging gold standard in CF care. To provide quantification—primarily in the context of research studies—scoring systems have been developed and validated to quantify extent and severity of the structural abnormalities (e.g., Brody [4], Helbich [5], PRAGMA-CF [6], Eichinger [7]). Since then, ultrashort echo-time ^{1}H magnetic resonance imaging (UTE MRI) of pediatric CF patients [8,9] has been shown to be amenable to CF image scoring [7,9,10], eliminating the need for ionizing-radiation exposure. While intrinsically subjective to some degree, structural image scoring predicts future pulmonary exacerbations [11,12] and lung function loss [13].

Functionally, multiple breath washout (MBW) has been shown to be more sensitive than ubiquitously used spirometry. MBW measures the number of lung turnovers, as defined by

the functional residual capacity, to reduce a tracer gas to a concentration of 2.5% of its initial value (lung clearance index; $LCI_{2.5}$). However, MBW lacks regional specificity needed to fully assess lung dysfunction [14]. To this end, hyperpolarized Xenon-129 ventilation MRI (^{129}Xe MRI) [15] shows promise in bridging the gaps between sensitivity, regionality, structure, and function.

^{129}Xe MRI determines the percent of lung volume which does not receive an adequate amount of gas following an inhalation (ventilation defect percentage, VDP). Both MBW [16,17] and ^{129}Xe MRI [18–21] have demonstrated sensitivity to early CF lung disease and treatment responses. However, each functional measurement may have a potential sensitivity bias towards certain structural abnormalities, which is important when considering clinical prognosis [22].

Thus, we compare functional measurements (spirometry, MBW, and ^{129}Xe MRI) to quantitative structural scores (UTE MRI) to determine the sensitivity of functional measures to structural defects in CF lung disease. We hypothesized both MBW and ^{129}Xe correlate more with mucus plugging and bronchial wall thickening compared to spirometry, as they are more common in mild disease and would lead to early ventilation heterogeneity. Additionally, we hypothesize these more sensitive functional/structural measurements would correlate better with 1-year outcomes (e.g., change in FEV_1 and number of pulmonary exacerbations requiring hospitalization) and would be dependent on modulator therapy usage.

Materials and Methods:

This prospective study was performed with approval from the IRB of Cincinnati Children's Hospital Medical Center and with oversight from the US-FDA under an investigational new drug (IND 123,577) protocol for hyperpolarized ^{129}Xe MRI. The study incorporated same-day assessment using four techniques: spirometry, MBW, ^{129}Xe MRI, and UTE MRI. This was performed in 27 modulator-naïve pediatric CF patients (ages 11.5±5.0; at least one copy of the *F508del* mutation; 15/12 M/F). Only pediatric subjects were assessed to limit to mild CF lung disease. Following the same-day assessment, patients were followed for 1 year per standard-of-care clinical assessments at our institution, and of the 27 subjects, 26 continued to be seen at our institution. Measured FEV_1 (frequency = 5.8±3.5/year) and hospitalizations due to pulmonary exacerbations were recorded from the electronic medical record for short-term outcomes. Average yearly change in FEV_1 (ΔFEV_1) and number of inpatient hospitalizations for pulmonary exacerbations (determined by a scoring system accounting for symptoms, lung exam findings, and FEV_1) were calculated. For ΔFEV_1, all clinically-acquired measurements were fit to a linear regression with the slope (in ΔFEV_1/year) taken as ΔFEV_1. Of the 26 subjects, 14 of the subjects began ivacaftor or double-modulator therapy (lumacaftor/ivacaftor–11 subjects, ivacaftor–2 subjects, and tezacaftor/ivacaftor–1 subject) within the year (mean start of 54 days after same-day assessment).

Spirometry (Koko, nSpire, Longmont, CO) and MBW (Exhalyzer D, EcoMedics, Duernten, Switzerland), were performed according to American Thoracic Society and European

Respiratory Society Guidelines [23,24]. MBW incorporated N_2 as the tracer gas, and the number of turnovers to reach a lung clearance index of 2.5% ($LCI_{2.5}$) was recorded.

Immediately following spirometry and MBW, the subjects underwent a single MRI session, during which ^{129}Xe and UTE MR images were acquired using a 3.0T Philips Achieva scanner and a homebuilt dual-loop coil for ^{129}Xe MRI [25] and a 32-channel cardiac coil for UTE MRI. ^{129}Xe images were acquired during a breath hold (~10 seconds, dependent on field of view, maximum of 16 seconds) of hyperpolarized ^{129}Xe gas equivalent to 1/6th the subjects predicted total lung capacity [26]. ^{129}Xe images were acquired as axial slices with a gradient recalled echo MRI sequence (3mm × 3mm × 15mm resolution). RF bias correction was completed by extracting and removing linear inhomogeneity profiles within the lung for all three dimensions. Ventilation defect percentage (VDP) was calculated using the linear binning method [27], with manual lung segmentation (D.J.R.) and a control cohort of healthy age-matched controls (23 subjects; ages 12.1±4.1; 13/10 M/F; ventilation = 0.54 ± 0.15). Structural information was obtained via UTE MRI, acquired with a 3D-radial MRI sequence with rectilinear encoding in the head-to-foot direction (stack-of-stars). The axial images were gated to end-expiration using a pencil-beam navigator (1.5mm × 1.5mm × 4.0mm resolution ≈5 minutes). Additional MRI parameters can be found in Table S1 of the Supplementary Materials. Thus, to acquire both structural and functional MRI images, less than 10 minutes was necessary.

Quantitative structural analysis of the UTE MRI was completed using a simplified Brody score [8]. The reader (M.M.W.), trained and certified for Brody scoring with 3 years of experience, was blinded to the subject/measurements obtained. The lung was divided into 6 lobar-regions (the lingula separated from the left lower lobe, for parallelism), each scored for mucus plugging, bronchial wall thickening, bronchiectasis, ground glass opacities, consolidations, air trapping and cysts. For each abnormality and lobe, a score of 0 to 2 was determined where 0 indicated not present, 1 indicates presence in <1/2 the lobe, and 2 indicates presence in >1/2 the lobe. Thus, the total possible abnormality score is 6 (lobes) × 7 (abnormalities) × 2 (extent) = 84. Additionally, since the Brody score is calculated for each lobe and structure, the distribution of structural abnormalities can be assessed by summing applicable scores.

For sensitivity to mild lung disease, upper/lower limits of normal (normal for 95% of a healthy population: mean ± 1.645×standard deviation or a z-score of ±1.645) were used as clinically-significant abnormality cutoffs and were calculated from the healthy control cohort (spirometry %-predicted values and VDP) or from previously published data (UTE score and $LCI_{2.5}$), as shown in Table 1 [8,28].

All functional measures were normally distributed according to the Shapiro-Wilk normality test (P   0.05); however, structural abnormality scores and number of pulmonary exacerbations were not. Thus, spearman correlations were used to compare structural abnormalities and lung function measurements, as well as their associations with clinical outcomes. A logistic regression was completed to calculated odds ratios. Two-tailed T-tests with unequal variances were implemented for comparisons of outcomes between groups. Statistical significance was determined by a P-value <0.05. Multiple testing correction for

significant correlations was completed using the Benjamini-Hochberg method with a Bonferonni α correction allowing for a 0.1 experimental false discovery rate to reduce Type I errors; P-values which are no longer significant are marked by an asterisk (*).

Results:

A summary of the data can be seen in Table 1 for all subjects and in Table S2 for modulator and modulator-naïve cohorts. Additionally, example results for 3 subjects can be seen in Figure 1. From spirometry, the average FEV_1 %-predicted of the cohort was 98.7±15.3% with only 3 subjects (11%) below 80%, the typical clinical abnormal function threshold, with one below our healthy cohort-derived lower limit of 70%. Similarly, the FEV_1/FVC ratio detected significant abnormality in 7%. Moving from percent predicted to GLI z-scores, spirometry results were more sensitive with 15%, 30%, and 22% of subjects having significantly abnormal lung function according to FEV_1, FEF_{25-75}, and FEV_1/FVC, respectively. Thus, GLI z-scores will be used for future analysis. MBW found a mean $LCI_{2.5}$ of 10.0±2.1 with an upper limit of normal (7.91) indicating abnormal lung function in 21 (78%) subjects. ^{129}Xe MRI analysis showed a VDP = 18.5±11.0% (ventilation = 0.42 ± 0.18) with an upper limit of normal (6.0%) indicating abnormal lung function in 23 (85%) subjects. The structural UTE MR images had a mean total score of 9.7±7.9 with the mean abnormality sub-scores ranging from 0.0 (cysts/bullae) up to 3.4 (bronchiectasis). The upper limit of 4.6 for the total score indicated 21 (78%) of the subjects had significant visible structural abnormalities.

Structurally, the right lung experienced more severe structural scores (average combined abnormality score of 5.9±4.4) than the left lung (3.9±3.8, P < 0.01). Additionally, the upper lobes displayed more severe structural disease (4.1±3.4) than the middle lobe/lingula (2.8±2.7, P < 0.01) and lower lobes (3.0±2.9, P < 0.01), in agreement with previous CT findings [4,29]. Notably, lobes with mucus plugs were strongly correlation with the occurrence of bronchiectasis and/or bronchial wall thickening. Eighty-nine percent of lobes with mucus plugging also exhibited more permanent structural airway changes, while only 37% of lobes lacking mucus plugging exhibited the bronchial abnormalities. This results in an odds ratio of 12.9 for more permanent airway structural changes given mucus plugging is visibly present in the same lobe (confidence interval = 4.3–39.0; P<0.0001).

Significant correlations between the functional measures (Table S3) were found (all P < 0.003). Variance between FEV_1 z-score, FEF_{25-75} z-score, and FEV_1/FVC z-score was minimal ($R^2 > 0.5$) as was the same for $LCI_{2.5}$ and VDP. However, correlations between spirometry and the newer functional measures all had an R^2 below 0.5.

Correlations of structural changes/severity with functional measurements were investigated to investigate which structural abnormalities most-influenced each functional metric (Table 2 and Figure 2). FEV_1/FVC z-score, $LCI_{2.5}$ and VDP correlated with the total structural abnormality score while FEV_1 and FEF_{25-75} z-scores did not. FEV_1 and FEF_{25-75} z-scores only correlated with ground glass opacities and consolidation/atelectasis abnormalities. FEV_1/FVC z-score correlated with mucus plugging and consolidation/atelectasis. $LCI_{2.5}$ and

VDP significantly correlated with mucus plugging while $LCI_{2.5}$ also correlated with bronchial wall thickening.

Correlations between the same-day assessment metrics and outcomes are shown in Table 3. Seven pulmonary exacerbations in 6 subjects were reported, with 4 occurring in subjects who started modulator therapy (P = 0.87). FEV_1 was only associated with VDP (P = 0.05*). For pulmonary exacerbations, the only significant correlation was bronchial wall-thickening (P=0.05*). However, there is a difference when considering modulator usage. For the subjects who began modulator therapy, we found three significant correlations (bronchial wall thickening, P < 0.01; bronchiectasis, P=0.01; and total Brody score, P = 0.03*).

Discussion:

In this study, we assessed multiple functional measurements in a group of pediatric CF patients and compared to same-day structural MRI findings. Additionally, clinical outcomes were analyzed to determine the relationship between structural/functional measurements to future FEV_1 and number of pulmonary exacerbations. This improves the ability for clinicians to select the appropriate test, interpret the results, and determine the best treatment/intervention in a personalized manner.

From the regional correlations between mucus plugging and bronchial changes, the odds ratio of 12.9 illustrates a likely causative relationship between mucus plugging and permanent airway structural changes and suggests that identifying and treating early mucus plugging with effective airway clearance and pharmaceutic interventions may yield long-term benefits. Additionally, while we used a simplified Brody scoring system, we suspect any validated CF scoring system [30] would show similar results. Moreover, while the structural scoring allowed for prognostic power with the ability to discriminate different abnormalities, it is currently a time-consuming process.

In agreement with previous publications, $LCI_{2.5}$ and VDP were more sensitive than FEV_1 at detecting mild disease [18–21]. This is demonstrated by $LCI_{2.5}$ and VDP detecting functional abnormalities in over 78% of the subjects despite mostly normal FEV_1 z-scores. This may be due to the sensitivity of $LCI_{2.5}$ and VDP to mucus plugging and bronchial abnormalities.

Additionally, an upper limit of normal for VDP is not well established and can vary depending on the cohort, acquisition methods, and precise quantitative analysis methods. Thus, the normal limit listed here is subject to change as this technique becomes more developed/standardized. Future refinements in analysis of ^{129}Xe MRI, will likely decrease variation within healthy subjects, lowering the limit of normal and increasing sensitivity. Thus, future studies should ensure consistent acquisition and analysis protocols. Lastly, previous studies showed moderate correlation between FEV_1 and total abnormality scores, but it was only significant when including subjects with abnormal spirometry [4]. Thus, the mild severity of disease in this cohort further emphasizes the sensitivity of $LCI_{2.5}$ and VDP compared to FEV_1.

There were some disagreements between the structural findings and the functional measurements. For example, subject 4 had the 7th highest VDP and 2nd highest $LCI_{2.5}$ but the structural score was average (16th highest). This is potentially due to the sensitivity of these functional scores to certain structural abnormalities as shown here. Subject 4's abnormalities were primarily present in mucus plugging and bronchial abnormalities with no ground glass, cysts, or air trapping observed which would explain the disagreement between VDP/$LCI_{2.5}$ and the structural scores. Additionally, the location of defects could lead to a disproportionate functional decline. For example, a mucus plug in a lobar bronchus would lead to a larger functional decline than one in a subsegmental bronchus.

While most of the variation in the functional measurements were not explained by structural measurements (max $R^2 = 0.28$), there was also noticeable variation in the correlations between functional measures (such as FEF_{25-75} z-score and VDP with an R^2 of 0.30). Since the correlations were not perfect between the functional measures, a potential sensitivity bias for each functional measure towards different structural abnormalities is likely, as supported by the functional measures being correlated with different structural abnormalities.

Transitioning onto modulator therapy was an effect modifier when investigating the correlations with pulmonary outcomes. None of the measurements acquired during the initial assessment (functional/structural scores) were different (all $P > 0.05$) between the modulator (n=14) and non-modulator (n=12) groups. Thus, prior to the 1-year observation, all structural and functional metrics were similar for the two cohorts. There is an expected reversal of non-permanent structural findings (i.e., mucus plugging), leaving only more permanent structural changes (i.e., bronchial damage) once modulator therapy is initiated. Thus, outcome associations are likely dependent on the abnormalities each technique is most sensitive. This effect modification resulted in the functional measurements (spirometry, $LCI_{2.5}$, and VDP) being poorly associated with 1 year outcomes. Associations of outcomes with UTE MRI scoring was also affected by modulator therapy, but since different types of abnormalities could be discriminated, we could observe that the more-permanent abnormalities were correlated for those who did initiate modulator therapy.

Another limitation of this study is the small number of pulmonary exacerbations in this cohort, likely due to the mild lung disease present in the pediatric CF population. While this increases the type II errors, the goal was to identify the most strongly correlated relationships between these measures. Despite this, statistically significant correlations were found but many more correlations likely exist. Future studies should consider including larger cohorts for an increased number of exacerbations or more sensitive outcome measures for improved sensitivity to smaller effects missed in this lower-powered study. Lastly, one of the modulator subjects who experienced a pulmonary exacerbation in the year following did not start their modulator until 286 days post-assessment (the last subject to initiate modulator therapy) and the exacerbation occurred before the start of the modulator therapy. However, adjusting for this does not change any conclusions within this study.

Our study suggests that $LCI_{2.5}$ and VDP may provide clinicians with earlier indicators of lung abnormalities. Furthermore, the association of mucus plugging with more permanent bronchial abnormalities suggests clinical interventions to prevent mucus plugs may prevent

progression of lung disease. As highly effective modulators become available to the broader CF population and approved for younger patients, we anticipate these sensitive tests will be important clinical tools to screen for pulmonary abnormalities and/or monitor lung function.

Conclusions:

$LCI_{2.5}$ from MBW and VDP from ^{129}Xe MRI were more sensitive to mild CF lung disease than spirometry—similar to that shown by others using ^{3}He MRI [20]. Reader scores of structural UTE MRI demonstrated the presence of mucus plugs in mild disease that correlated with structural bronchial changes (and irreversible lung-function declines). The significant correlations for MBW and ^{129}Xe MRI with mucus plugging—more common in earlier CF lung disease—are probable reasons for increased sensitivity to mild lung function decline. More permanent abnormalities (bronchiectasis and bronchial wall thickening) are associated with exacerbations for those who began modulator therapy. These findings suggest functional imaging could be used for screening, due to its sensitivity, and structural imaging can also be used in determination of interventions/treatments. Thus, the use of tomographic imaging to visualize both structural (UTE MRI or CT) and functional (^{129}Xe MRI) abnormalities will likely benefit future studies/clinical decisions in the coming age of milder lung disease in cystic fibrosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

References:

[1]. Calder AD, Bush A, Brody AS, Owens CM. Scoring of chest CT in children with cystic fibrosis: state of the art. Pediatr Radiol 2014;44:1496–506. 10.1007/s00247-013-2867-y. [PubMed: 25164326]

[2]. Ronan NJ, Einarsson GG, Twomey M, Mooney D, Mullane D, NiChroinin M, et al. CORK Study in Cystic Fibrosis: Sustained Improvements in Ultra-Low-Dose Chest CT Scores After CFTR Modulation With Ivacaftor. Chest 2018;153:395–403. 10.1016/j.chest.2017.10.005. [PubMed: 29037527]

[3]. Taylor-Cousar JL, Mall MA, Ramsey BW, McKone EF, Tullis E, Marigowda G, et al. Clinical development of triple-combination CFTR modulators for cystic fibrosis patients with one or two F508del alleles. ERJ Open Res 2019;5:00082–2019. 10.1183/23120541.00082-2019. [PubMed: 31218221]

[4]. Brody AS, Klein JS, Molina PL, Quan J, Bean JA, Wilmott RW. High-resolution computed tomography in young patients with cystic fibrosis: Distribution of abnormalities and correlation with pulmonary function tests. J Pediatr 2004;145:32–8. 10.1016/j.jpeds.2004.02.038. [PubMed: 15238903]

[5]. Helbich TH, Heinz-Peer G, Eichler I, Wunderbaldinger P, Götz M, Wojnarowski C, et al. Cystic Fibrosis: CT Assessment of Lung Involvement in Children and Adults. Radiology 1999;213:537–44. 10.1148/radiology.213.2.r99nv04537. [PubMed: 10551238]

[6]. Rosenow T, Oudraad MCJ, Murray CP, Turkovic L, Kuo W, de Bruijne M, et al. PRAGMA-CF. A Quantitative Structural Lung Disease Computed Tomography Outcome in Young Children with

Cystic Fibrosis. Am J Respir Crit Care Med 2015;191:1158–65. 10.1164/rccm.201501-0061OC. [PubMed: 25756857]

[7]. Eichinger M, Optazaite D-E, Kopp-Schneider A, Hintze C, Biederer J, Niemann A, et al. Morphologic and functional scoring of cystic fibrosis lung disease using MRI. Eur J Radiol 2012;81:1321–9. 10.1016/j.ejrad.2011.02.045. [PubMed: 21429685]

[8]. Roach DJ, Crémillieux Y, Fleck RJ, Brody AS, Serai SD, Szczesniak RD, et al. Ultrashort Echo-Time Magnetic Resonance Imaging Is a Sensitive Method for the Evaluation of Early Cystic Fibrosis Lung Disease. Ann Am Thorac Soc 2016;13:1923–31. 10.1513/AnnalsATS.201603-203OC. [PubMed: 27551814]

[9]. Dournes G, Yazbek J, Benhassen W, Benlala I, Blanchard E, Truchetet ME, et al. 3D ultrashort echo time MRI of the lung using stack-of-spirals and spherical k-Space coverages: Evaluation in healthy volunteers and parenchymal diseases. J Magn Reson Imaging 2018;48:1489–97. 10.1002/jmri.26212. [PubMed: 30203889]

[10]. Dournes G, Menut F, Macey J, Fayon M, Chateil J, Salel M, et al. Lung morphology assessment of cystic fibrosis using MRI with ultra-short echo time at submillimeter spatial resolution. Eur Radiol 2016;26:3811–20. 10.1007/s00330-016-4218-5. [PubMed: 26843010]

[11]. Brody AS, Sucharew H, Campbell JD, Millard SP, Molina PL, Klein JS, et al. Computed tomography correlates with pulmonary exacerbations in children with cystic fibrosis. Am J Respir Crit Care Med 2005;172:1128–32. 10.1164/rccm.200407-989OC. [PubMed: 16100015]

[12]. Sanders DB, Li Z, Brody AS. Chest computed tomography predicts the frequency of pulmonary exacerbations in children with cystic fibrosis. Ann Am Thorac Soc 2015;12:64–9. 10.1513/AnnalsATS.201407-338OC. [PubMed: 25474182]

[13]. Schaefer JF, Hector A, Schmidt K, Teufel M, Fleischer S, Graepler-Mainka U, et al. A semiquantitative MRI-Score can predict loss of lung function in patients with cystic fibrosis: Preliminary results. Eur Radiol 2018;28:74–84. 10.1007/s00330-017-4870-4. [PubMed: 28664245]

[14]. Subbarao P, Milla C, Aurora P, Davies JC, Davis SD, Hall GL, et al. Multiple-Breath Washout as a Lung Function Test in Cystic Fibrosis. A Cystic Fibrosis Foundation Workshop Report. Ann Am Thorac Soc 2015;12:932–9. 10.1513/AnnalsATS.201501-021FR. [PubMed: 26075554]

[15]. Couch MJ, Thomen R, Kanhere N, Hu R, Ratjen F, Woods J, et al. A two-center analysis of hyperpolarized 129Xe lung MRI in stable pediatric cystic fibrosis: Potential as a biomarker for multi-site trials. J Cyst Fibros 2019;18:728–33. 10.1016/j.jcf.2019.03.005. [PubMed: 30922812]

[16]. Amin R, Stanojevic S, Kane M, Webster H, Ratjen F. A randomized controlled trial to evaluate the lung clearance index as an outcome measure for early phase studies in patients with cystic fibrosis. Respir Med 2016;112:59–64. 10.1016/j.rmed.2016.01.020. [PubMed: 26856191]

[17]. Subbarao P, Stanojevic S, Brown M, Jensen R, Rosenfeld M, Davis S, et al. Lung Clearance Index as an Outcome Measure for Clinical Trials in Young Children with Cystic Fibrosis. A Pilot Study Using Inhaled Hypertonic Saline. Am J Respir Crit Care Med 2013;188:456–60. 10.1164/rccm.201302-0219OC. [PubMed: 23742699]

[18]. Svenningsen S, Kirby M, Starr D, Leary D, Wheatley A, Maksym GN, et al. Hyperpolarized 3He and 129Xe MRI: Differences in asthma before bronchodilation. J Magn Reson Imaging 2013;38:1521–30. 10.1002/jmri.24111. [PubMed: 23589465]

[19]. Thomen RP, Sheshadri A, Quirk JD, Kozlowski J, Ellison HD, Szczesniak RD, et al. Regional Ventilation Changes in Severe Asthma after Bronchial Thermoplasty with 3He MR Imaging and CT. Radiology 2015;274:250–9. 10.1148/radiol.14140080. [PubMed: 25144646]

[20]. Marshall H, Horsley A, Taylor CJ, Smith L, Hughes D, Horn FC, et al. Detection of early subclinical lung disease in children with cystic fibrosis by lung ventilation imaging with hyperpolarised gas MRI. Thorax 2017;72. 10.1136/thoraxjnl-2016-208948.

[21]. Rayment JH, Couch MJ, McDonald N, Kanhere N, Manson D, Santyr G, et al. Hyperpolarised 129 Xe magnetic resonance imaging to monitor treatment response in children with cystic fibrosis. Eur Respir J 2019;53:1802188. 10.1183/13993003.02188-2018. [PubMed: 30819815]

[22]. Thomen RP, Walkup LL, Roach DJ, Higano N, Schapiro A, Brody A, et al. Regional Structure-function in Cystic Fibrosis Lung Disease Using Hyperpolarized 129Xe and Ultrashort Echo

Magnetic Resonance Imaging. Am J Respir Crit Care Med 2020:rccm.202001–0031LE. 10.1164/rccm.202001-0031LE.

[23]. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319–38. 10.1183/09031936.05.00034805. [PubMed: 16055882]

[24]. Robinson PD, Latzin P, Verbanck S, Hall GL, Horsley A, Gappa M, et al. Consensus statement for inert gas washout measurement using multiple- and single- breath tests. Eur Respir J 2013;41:507–22. 10.1183/09031936.00069712. [PubMed: 23397305]

[25]. Loew W, Thomen RP, Giaquinto R, Pratt R, Cleveland ZI, Walkup LL, et al. A dual loop T/R-xenon coil for homogenous excitation with improved comfort and size. Proc. 24th Annu. Meet ISMRM, Singapore, 2016.

[26]. Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity: ATS Workshop on Lung Volume Measurements Official Statement of the European Respiratory Society. Eur Respir J 1995;8:492–506. 10.1183/09031936.95.08030492. [PubMed: 7789503]

[27]. He M, Driehuys B, Que LG, Huang YCT. Using Hyperpolarized 129Xe MRI to Quantify the Pulmonary Ventilation Distribution. Acad Radiol 2016;23:1521–31. 10.1016/j.acra.2016.07.014. [PubMed: 27617823]

[28]. Anagnostopoulou P, Latzin P, Jensen R, Stahl M, Harper A, Yammine S, et al. Normative data for multiple breath washout outcomes in school-aged Caucasian children. Eur Respir J 2020;55. 10.1183/13993003.01302-2019.

[29]. Li Z, Sanders DB, Rock MJ, Kosorok MR, Collins J, Green CG, et al. Regional differences in the evolution of lung disease in children with cystic fibrosis. Pediatr Pulmonol 2012;47:635–40. 10.1002/ppul.21604. [PubMed: 22162514]

[30]. De Jong PA, Tiddens HAWM. Cystic fibrosis-specific computed tomography scoring. Proc Am Thorac Soc 2007;4:338–42. 10.1513/pats.200611-175HT. [PubMed: 17652497]

Highlights:

- $LCI_{2.5}$, [129]Xe VDP, and UTE more sensitive to pediatric CF disease than spirometry

- [1]H MRI suggests increased odds for airway damage in lobes with mucus plugging

- Most spirometry measures correlated with consolidations and ground glass

- $LCI_{2.5}$ and [129]Xe VDP correlated with mucus plugging

- Increased exacerbations most strongly correlated with mucus plugs and airway damage
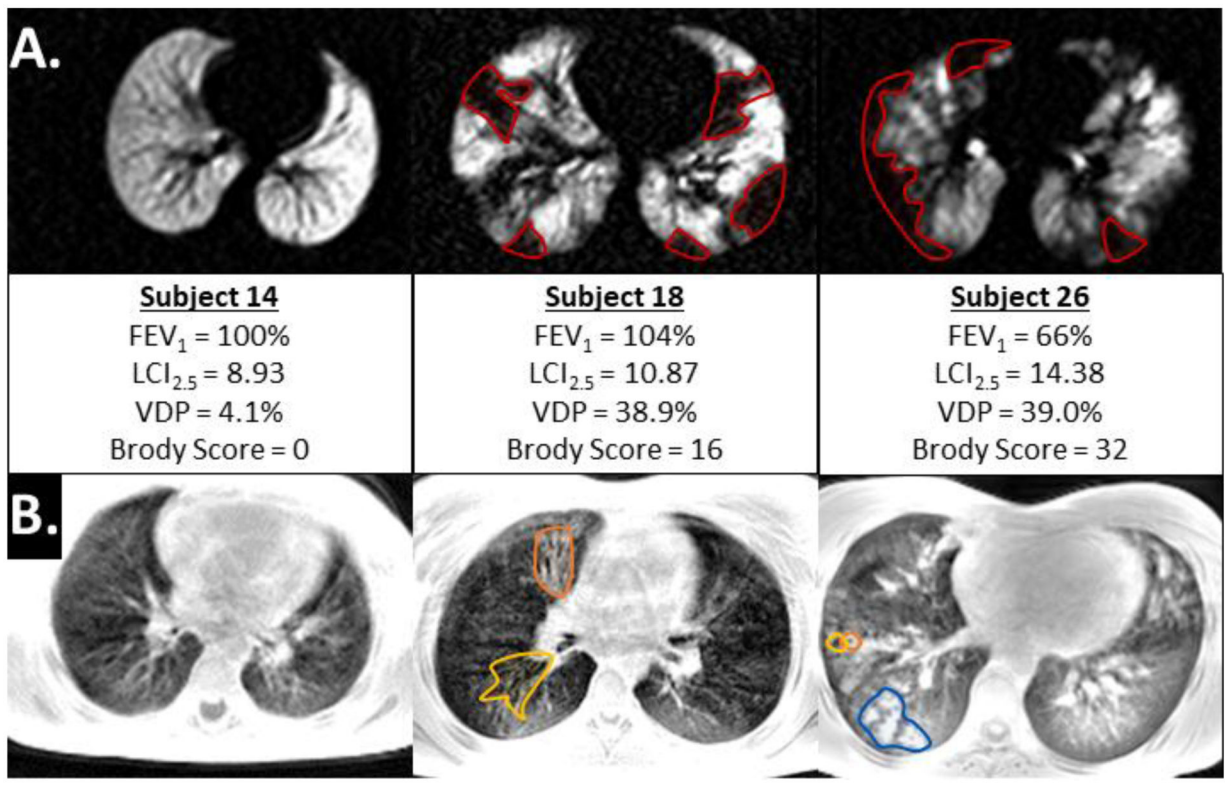
Figure 1:

Example image slices for ^{129}Xe (a.) and UTE (b.) images in CF subjects. Subject 14 (left) is an example of a subject a relatively healthy subject with only LCI$_{2.5}$ being slightly elevated. Subject 18 (middle) is an example of a subject with elevated LCI$_{2.5}$, VDP and structural abnormalities despite normal FEV$_1$. Subject 26 (right) is an example subject who also had an abnormal FEV$_1$ %-predicted. In (a.), regions circled in red illustrate examples of ventilation defects and in (b.), example regions are circled in orange for combined bronchiectasis/wall thickening, yellow for only bronchiectasis and blue for mucus plugging. Each image provides the subject's FEV$_1$ %-predicted, LCI$_{2.5}$, VDP, and Brody score.

Figure 2:
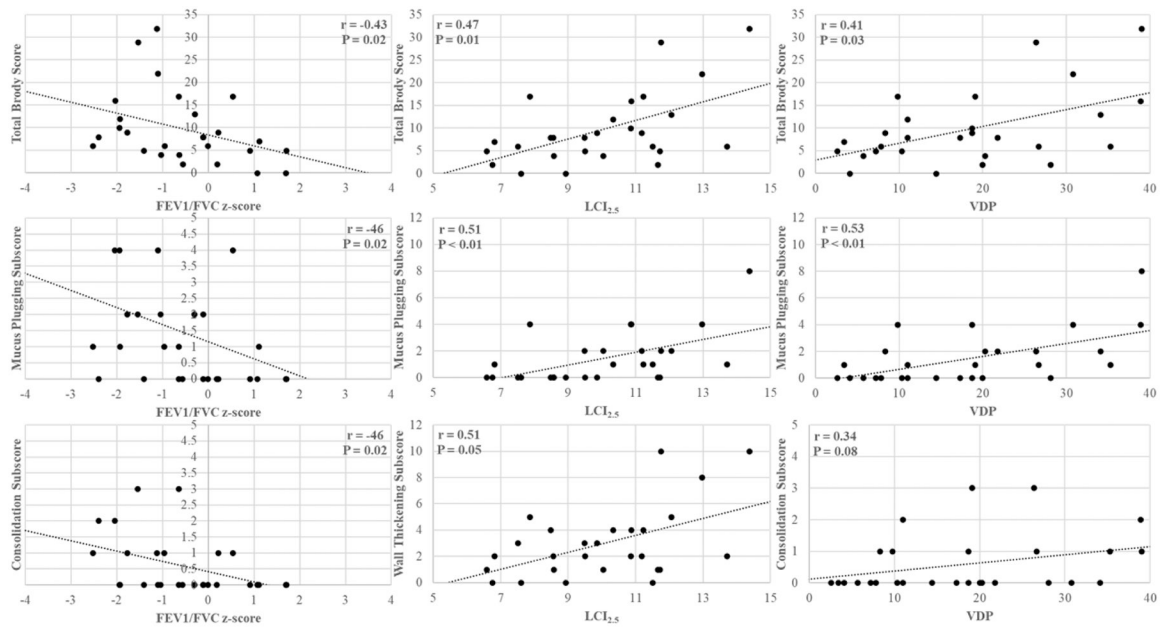Select correlations between structural scores and the functional measurements - FEV$_1$/FVC z-score (left column), LCI (middle column), and VDP (right column). Dots correspond to subjects and the dashed line shows the linear regression.

Table 1:

Demographic, same-day assessment results, and short-term outcomes for the cohort.

	Mean	Standard Deviation	Range	Limit of Normal	Percent Abnormal
Demographics					
Gender	15M/12F	-	-	-	-
Age	11.9	4.9	6.0–20.5	-	-
Same-day Assessment (N=27)					
FEV$_1$ %-predicted	98.7%	15.3%	66–131%	>70%	4%
FEV$_1$ GLI z-score	−0.32	1.25	−3.07–2.60	>−1.645	15%
FEF$_{25-75}$ %-predicted	92.9%	33.3%	47–147%	-	-
FEF$_{25-75}$ GLI z-score	−0.55	1.41	−2.96–2.22	>−1.645	30%
FEV1/FVC	84.7%	8.1%	70–99%	>73%	7%
FEV1/FVC GLI z-score	−0.54	1.19	−2.52–1.71	>−1.645	22%
LCI$_{2.5}$	10.0	2.1	6.6–14.4	<7.91	78%
VDP	18.5%	11.0%	2.6–38.9%	<6.0%	85%
Total Brody Score	9.7	7.9	0–32	<4.6	78%
Mucus Plugging	1.4	1.9	0–8	-	-
Bronchial Wall Thickening	3.0	2.7	0–10	-	-
Bronchiectasis	3.4	2.5	0–10	-	-
Ground Glass	0.4	0.9	0–3	-	-
Consolidation/Atelectasis	0.6	0.9	0–3	-	-
Air Trapping	0.9	1.0	0–4	-	-
Cysts/Bullae	0.0	0.2	0–1	-	-
1 Year Outcomes (N=26)					
FEV$_1$ (%/year)	2.4	11.7	−27.6–19.2	-	-
# Pulmonary Exacerbations	0.27	0.52	0–2	-	-

Row headings in italics denote structural sub scores which make up the total Brody score. The limits of normal were derived as described in the text. Missing areas represent either not applicable or available value

Table 2:

Spearman *r* and P-value for correlations between structural abnormality scores from UTE MRI and functional measures from spirometry, MBW, and ^{129}Xe MRI.

	FEV$_1$ z-score	FEF$_{25-75}$ z-score	FEV$_1$/FVC z-score	LCI$_{2.5}$	VDP
Total Brody Score	*r* = −0.31 (P = 0.12)	*r* = −0.35 (P = 0.07)	**r = −0.44 (P = 0.02)**	**r = 0.47 (P = 0.01)**	**r = 0.41 (P = 0.03[*])**
Mucus Plugging	*r* = −0.23 (P = 0.23)	*r* = −0.33 (P = 0.10)	**r = −0.45 (P = 0.02)**	**r = 0.51 (P < 0.01)**	**r = 0.53 (P <0.01)**
Bronchial Wall Thickening	*r* = −0.16 (P = 0.43)	*r* = −0.17 (P = 0.40)	*r* = −0.27 (P = 0.17)	**r = 0.39 (P =0.05[*])**	*r* = 0.32 (P = 0.10)
Bronchiectasis	*r* = −0.14 (P = 0.50)	*r* = −0.14 (P = 0.49)	*r* = −0.21 (P = 0.30)	*r* = 0.36 (P = 0.07)	*r* = 0.33 (P = 0.09)
Ground Glass	**r = −0.44 (P = 0.02)**	**r = −0.47 (P = 0.01)**	*r* = −0.30 (P = 0.12)	*r* = 0.09 (P = 0.66)	*r* = −0.00 (P = 0.98)
Consolidation/Atelectasis	**r = −0.46 (P = 0.02)**	**r = −0.45 (P = 0.02)**	**r = −0.46 (P = 0.02)**	*r* = 0.35 (P = 0.07)	*r* = 0.34 (P = 0.08)
Air Trapping	*r* = −0.10 (P = 0.55)	*r* = −0.19 (P = 0.33)	*r* = −0.27 (P = 0.17)	*r* = 0.28 (P = 0.16)	*r* = 0.12 (P = 0.95)
Cysts/Bullae	*r* = 0.09 (P = 0.66)	*r* = 0.16 (P = 0.41)	*r* = 0.18 (P = 0.38)	*r* = −0.03 (P = 0.90)	*r* = 0.01 (P = 0.95)

Statistically significant correlations are in bold.

[*] indicates no longer significant after correction for multiple tests.

Table 3:

Spearman *r* and P-value for correlations between quantitative functional and structural scores with outcomes including the yearly change in FEV_1 and number of pulmonary exacerbations for the year following the same-day assessment.

	Cohort	FEV_1	# Pulmonary Exacerbations
FEV_1 z-score	All	$r = -0.18$ (P = 0.38)	$r = -0.23$ (P = 0.25)
	Modulator	$r = -0.36$ (P = 0.20)	$r = -0.16$ (P = 0.59)
	No Modulator	$r = 0.10$ (P = 0.74)	$r = -0.42$ (P = 0.18)
FEF_{25-75} z-score	All	$r = -0.21$ (P = 0.30)	$r = -0.21$ (P = 0.30)
	Modulator	$r = -0.36$ (P = 0.20)	$r = -0.26$ (P = 0.38)
	No Modulator	$r = 0.04$ (P = 0.91)	$r = -0.25$ (P = 0.44)
FEV_1/FVC z-score	All	$r = -0.08$ (P = 0.68)	$r = -0.13$ (P = 0.51)
	Modulator	$r = -0.20$ (P = 0.48)	$r = -0.27$ (P = 0.34)
	No Modulator	$r = 0.12$ (P = 0.71)	$r = -0.02$ (P = 0.96)
$LCI_{2.5}$	All	$r = 0.12$ (P = 0.57)	$r = 0.19$ (P = 0.36)
	Modulator	$r = 0.46$ (P = 0.09)	$r = 0.04$ (P = 0.89)
	No Modulator	$r = -0.34$ (P = 0.29)	$r = 0.35$ (P = 0.26)
VDP	All	**$r = -0.39$ (P = 0.05 [*])**	$r = 0.28$ (P = 0.17)
	Modulator	$r = -0.44$ (P = 0.12)	$r = 0.27$ (P = 0.34)
	No Modulator	$r = -0.44$ (P = 0.15)	$r = 0.35$ (P = 0.26)
Total Brody Score	All	$r = -0.03$ (P = 0.90)	$r = 0.30$ (P = 0.13)
	Modulator	$r = 0.25$ (P = 0.39)	**$r = 0.57$ (P = 0.03 [*])**
	No Modulator	$r = -0.33$ (P = 0.30)	$r = 0.06$ (P = 0.85)
Mucus Plugging	All	$r = -0.10$ (P = 0.61)	$r = 0.08$ (P = 0.70)
	Modulator	$r = 0.35$ (P = 0.23)	$r = 0.15$ (P = 0.60)
	No Modulator	$r = -0.42$ (P = 0.17)	$r = 0.15$ (P = 0.63)
Bronchial Wall Thickening	All	$r = -0.12$ (P = 0.56)	**$r = 0.39$ (P = 0.05 [*])**
	Modulator	$r = 0.10$ (P = 0.74)	**$r = 0.71$ (P < 0.01)**
	No Modulator	$r = -0.31$ (P = 0.33)	$r = 0.08$ (P = 0.79)
Bronchiectasis	All	$r = -0.17$ (P = 0.40)	$r = 0.34$ (P = 0.09)
	Modulator	$r = 0.08$ (P = 0.80)	**$r = 0.65$ (P = 0.01)**
	No Modulator	$r = -0.44$ (P = 0.15)	$r = 0.06$ (P = 0.85)
Ground Glass	All	$r = 0.34$ (P = 0.09)	$r = 0.24$ (P = 0.25)
	Modulator	$r = 0.46$ (P = 0.10)	$r = 0.23$ (P = 0.44)
	No Modulator	$r = 0.32$ (P = 0.32)	$r = 0.32$ (P = 0.31)
Consolidation/Atelectasis	All	$r = 0.07$ (P = 0.73)	$r = 0.15$ (P = 0.46)
	Modulator	$r = 0.17$ (P = 0.57)	$r = 0.11$ (P = 0.71)
	No Modulator	$r = -0.18$ (P = 0.57)	$r = 0.20$ (P = 0.52)
Air Trapping	All	$r = 0.06$ (P = 0.75)	$r = -0.31$ (P = 0.13)
	Modulator	$r = 0.23$ (P = 0.43)	$r = -0.21$ (P = 0.46)
	No Modulator	$r = -0.29$ (P = 0.36)	$r = -0.42$ (P = 0.17)

	Cohort	FEV$_1$	# Pulmonary Exacerbations
	All	$r = 0.01$ (P = 0.95)	$r = 0.35$ (P = 0.08)
Cysts/Bullae	Modulator	$r = -0.03$ (P = 0.91)	$r = 0.44$ (P = 0.12)
	No Modulator	N/A[*]	N/A[*]

Statistics are given for the entire cohort, those who started a modulator therapy the following year (n=14), and those who did not (n=12). Statistically significant correlations are in bold.

[*] indicates no longer significant after correction for multiple tests.

[*] N/A indicates inability to calculate due to all subjects having the same value (0, not present).