Original Research

Differences in Hyperpolarized ^{3}He Ventilation Imaging After 4 Years in Adults With Cystic Fibrosis

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Purpose: To evaluate cystic fibrosis (CF) subjects over 4 years using ^{3}He magnetic resonance imaging (MRI), pulmonary function tests, and track hospitalization and physician visits.

Materials and Methods: Five CF adults provided written informed consent to an approved protocol and underwent MRI, spirometry, and plethysmography at baseline, 7 days, and 4 ± 1 years later. ^{3}He MRI ventilation defect percent (VDP) was generated for all subjects and timepoints.

Results: After 4 years, mean forced expiratory volume in 1 second / forced vital capacity (FEV_1/FVC) was lower ($P = 0.01$) in all subjects and there were no other pulmonary function test changes. Two CF adults showed significantly elevated (worse) ^{3}He VDP at baseline and after 4 years they had significantly greater (worsened) VDP ($P = 0.02$), without a significant FEV_1 decline ($P = 0.06$) but with a greater number of exacerbations ($P < 0.05$). Baseline VDP strongly correlated with FEV_1 ($r^2 = 0.98$, $P = 0.0007$) at 4-year follow-up.

Conclusion: For two CF subjects, VDP was significantly worse at baseline and worsened over 4 years, which was in agreement with a greater number of hospitalizations and clinic visits. These results are limited by the very small sample size, but the strong VDP correlation with longitudinal changes in FEV_1 generates the hypothesis that abnormal VDP may temporally precede FEV_1 decline in CF subjects; this must be tested in a larger CF study.

Key Words: magnetic resonance imaging; hyperpolarized gas; ^{3}He; cystic fibrosis; lung disease
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CYSTIC FIBROSIS (CF) is an autosomal recessive, multiorgan disease, resulting in impaired chloride permeability of epithelial cells in the lungs, digestive system, and sweat glands (1). The major pulmonary manifestations of CF are mucus plugging, sputum buildup, and chronic lung infection, resulting in progressive pulmonary disease and lung function decline—the main cause of morbidity and mortality in CF patients (2). The forced expiratory volume in 1 second (FEV_1), measured using spirometry, is the most commonly used measurement for evaluating CF severity and disease progression (3). However, spirometry measurements only weakly correlate with symptom scores, are insensitive to the pathophysiological changes associated with disease progression, and, importantly, do not correlate well with patient outcomes (4). As the median survival age for CF patients continues to increase, sensitive and objective quantitative measures of disease progression are needed to help guide therapy decisions, especially during exacerbations, and to help stratify patients for potential lung transplantation (5).

In this context, imaging measurements have the potential to provide a way to monitor CF lung disease progression because they provide direct, quantitative, and regional information related to the pulmonary pathologies related to disease worsening. For example, x-ray computed tomography (CT) (6,7), positron emission tomography (PET) (8), and magnetic resonance imaging (MRI) (9,10) have been previously used to visualize and estimate CF pulmonary structure and function. While CT measurements have been used as surrogate endpoints in clinical trials (6,11), the ionizing radiation associated with CT still limits serial and longitudinal use, particularly in pediatric CF patients (12). In contrast, MR methods do not pose a radiation

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risk and recent hyperpolarized ^{3}He MRI evaluations of pediatric and adult CF have revealed pulmonary ventilation abnormalities in patients with relatively normal FEV_1 (13). Both novel and conventional ^{1}H MRI has also been used to detect and measure lung perfusion and structural abnormalities (14–16), as well as pulmonary response to CF therapy (17,18). Despite excellent progress and the fact that ^{3}He MRI has been under development for over two decades, its rich informative content has not been exploited in longitudinal evaluations of CF subjects. Therefore, our objective here was to evaluate hyperpolarized ^{3}He MRI ventilation abnormalities, pulmonary function test measurements, and the frequency of exacerbations for five adults with CF followed over 4 years.

MATERIALS AND METHODS

Study Design

All subjects provided written informed consent to a study protocol approved by a local research ethics board and Health Canada, and the study was compliant with the Health Insurance Portability and Accountability Act. Five subjects (three males) with CF were recruited between the ages of 20 and 36 years (28 ± 6 years), without claustrophobia or MRI contraindications and with a baseline $FEV_1\%_{pred} > 60\%$ on their first visit. All subjects were evaluated at baseline, 7 days later, and at a 4-year follow-up visit; the baseline and 7-day short-term variability of ^{3}He MRI was previously reported (9). Follow-up visits were scheduled when subjects were stable, and at least 8 weeks postexacerbation. Retrospective analysis showed that study visits were at least 8 weeks pre- and postexacerbation in these study subjects. Spirometry and plethysmography was performed 30 minutes prior to MRI. Hospitalization and physician visits related to pulmonary CF disease were obtained using PowerChart (Cerner, Kansas City, MO).

Pulmonary Function Tests

Spirometry and plethysmography were performed at all three timepoints using the average of three breathing maneuvers or the best effort using a *Medgraphics Elite Series* plethysmograph (MedGraphics, St. Paul, MN) and in accordance with American Thoracic Society guidelines (19). The values reported are inherently normalized for healthy subject age, sex, and height and reported as percent predicted values using onboard software on the plethysmography unit.

Imaging

MRI was performed as previously described (9) on a 3.0T Discovery MR750 (General Electric Health Care, Milwaukee, WI) system. ^{3}He gas was polarized to 30–40% using a turn-key, spin-exchange polarizer system (HeliSpin, Polarean, Durham, NC) as previously described (20) and doses (5 mL/kg body weight) were administered in 1.0 L Tedlar bags diluted with medical grade nitrogen (N_2). In order to minimize potential differences in the level of inspiration between breath-hold scans, practice inspiration breath-holds were conducted outside the scanner using 1.0 L Tedlar bags filled with room air. Subjects were also coached at the scanner by a pulmonary function technologist during all inspiration breath-hold scans.

Thoracic CT was acquired on a 64-slice Lightspeed VCT scanner (GEHC) (64×0.625 mm, 120 kVp, 100 effective mA, tube rotation time of 500 msec, and a pitch of 1.0). A single spiral acquisition of the entire lung was acquired from the apex to the base with subjects in the supine position and in breath-hold after inhalation of a 1.0 L $^4He/N_2$ mixture from functional residual capacity (FRC). Images were reconstructed using a slice thickness of 1.25 mm with a standard convolution kernel. The radiation dose related to CT imaging was calculated according to manufacturer settings using the ImPACT CT patient dosimetry calculator based on the Health Protection Agency (UK) NRPB-SR250. The total effective dose for an average adult was 1.8 mSv.

Ventilation defect percent (VDP) measurements were generated in duplicate by two observers (G.P. and S.S) with 1–4 years experience, blinded to subject and timepoint, using semiautomated segmentation software as previously described (21). ^{3}He MRI difference maps were generated by coregistering ^{3}He center slices from the baseline and 4-year follow-up visits using landmark-based affine image registration with 4–7 fiducial markers. Temporal difference maps were generated from coregistered voxels for six center slices, based on four clusters that described: 1) persistent ventilation defects (black), 2) persistent ventilation (cyan), 3) new ventilation defects (red), and 4) newly ventilated regions (green).

Statistics

For all statistical analyses, VDP results generated by a single observer (S.S) were used. Measurement comparisons were performed using a Wilcoxon matched-pairs two-tailed *t*-test using IBM SPSS Statistics 20.00 (SPSS, Chicago, IL). Relationships between VDP and FEV_1 were evaluated using linear regression (R^2) analysis (least squares method) performed using GraphPad Prism 4.01 (GraphPad Software, La Jolla, CA; 2004); best fit lines and the corresponding 95% confidence bands were determined. Results were considered statistically significant when the probability of making a Type I error was less than 5% ($P < 0.05$).

RESULTS

All five CF subjects were evaluated 4 ± 1 years after a baseline visit (three males, mean age $= 28 \pm 7$ years, body mass index [BMI] $= 26 \pm 3$ kg/m^2). As shown in a subject listing in Table 1, at baseline the FEV_1 was $76 \pm 17\%_{pred}$, forced vital capacity (FVC) was $87 \pm 17\%_{pred}$, functional residual capacity (FRC) was $108 \pm 34\%_{pred}$, inspiratory capacity (IC) was $108 \pm 28\%_{pred}$, and residual volume normalized to total lung capacity (RV/TLC) was $147 \pm 37\%_{pred}$. Figure 1 shows the coronal center slice ^{3}He MRI coregistered to ^{1}H anatomical MRI for all subjects and visits.

Table 1
Subject Listing of Measurements for Baseline, 7-Day, and 4-Year Follow-Up Visits

	Visit Date	BMI (kg/m^2)	FEV_1 ($\%_{pred}$)	FVC ($\%_{pred}$)	FEV_1/FVC (%)	IC ($\%_{pred}$)	FRC ($\%_{pred}$)	RV ($\%_{pred}$)	TLC ($\%_{pred}$)	RV/TLC ($\%_{pred}$)	DL_{CO} ($\%_{pred}$)	VDP (%) Obs.1/ Obs.2	Clinic/ Hospital Rate	Exacerbation Rate
Subject 1														
BL	2/21/2008	24	74	75	87	ND	ND	ND	ND	ND	ND	11/14	1.55	0.38
7 day	2/28/2008	24	79	78	88	ND	ND	ND	ND	ND	ND	9/9		
4 yr	4/3/2013	22	73	78	80	83	103	120	94	134	85	11/12		
Subject 2														
BL	8/20/2008	26	81	103	63	99	156	221	128	128	100	25/26	4.29	1.71
7 day	8/25/2008	26	78	96	65	118	166	270	140	191	105	30/29		
4 yr	4/9/2013	24	58	91	51	86	178	304	132	231	103	41/46		
Subject 3														
BL	9/28/2008	28	79	90	79	97	95	134	96	144	100	8/7	1.96	0.00
7 day	10/4/2008	28	75	89	71	90	99	109	94	120	ND	7/8		
4 yr	4/11/2013	28	81	92	72	115	92	122	104	117	114	4/3		
Subject 4														
BL	9/9/2009	30	50	65	62	87	105	189	96	200	87	34/32	3.00	1.91
7 day	9/16/2009	30	51	70	59	90	106	163	98	168	101	35/33		
4 yr	5/8/2013	29	41	59	56	72	128	198	100	178	85	45/43		
Subject 5														
BL	1/14/2010	22	96	103	81	149	77	125	110	117	94	1/2	2.15	0.31
7 day	1/20/2010	22	95	102	81	127	80	90	101	92	104	1/2		
4 yr	4/5/2013	22	96	104	79	118	100	108	108	99	105	1/2		
Mean (SD)														
BL		26 (3)	76 (16)	87 (17)	74 (11)	108 (28)	108 (34)	167 (46)	107 (15)	147 (37)	95 (6)	15 (13)	2.59 (1.09)	0.86 (0.88)
7 day		26 (3)	76 (16)	87 (13)	73 (12)	106 (19)	113 (37)	158 (81)	108 (21)	143 (45)	103 (2)	16 (15)		
4 yr		25 (3)	69 (21)	84 (17)	67 (13)	94 (21)	120 (35)	170 (83)	107 (15)	151 (53)	98 (13)	21 (22)		

ND, not determined; SD, standard deviation; $\%_{pred}$, percent predicted; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IC, inspiratory capacity; FRC, functional residual capacity; RV, reserve volume; TLC, total lung capacity; DL_{CO}, carbon monoxide diffusion capacity of the lung; VDP, ventilation defect percent; Obs, observer (1 or 2); Clinic/Hospital Rate, average clinic visits and hospitalization per year during study duration; Exacerbation Rate, average exacerbations per year during study duration; BL, baseline; 4yr, 4-years.

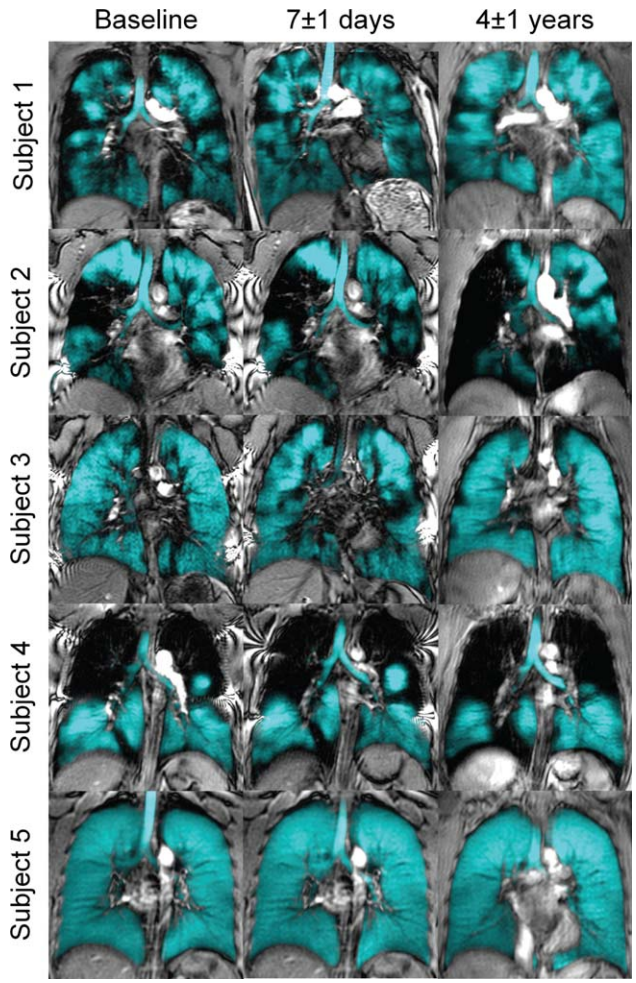

Figure 1. Hyperpolarized ^{3}He MRI gas distribution for all subjects. Coronal center-slice ^{3}He MRI (blue) coregistered to the corresponding anatomical ^{1}H MRI (gray) for all subjects and visits. Ventilation defect percent (VDP) for each subject at baseline, 7-day, and 4-year follow-up were: S1) 11, 9 and 11; S2) 25, 30, and 41; S3) 8, 7, and 4; S4) 34, 35, and 45; and S5) 1, 1, and 1.

There were large focal defects present at all three timepoints for Subjects 2 and 4, whereas for Subjects 1 and 3 there was a heterogeneous ventilation pattern. In contrast, for Subject 5 there was homogenous ventilation with no ventilation defects.

As shown in Table 1, there was no mean change in VDP or pulmonary function measurements with the exception of FEV_1/FVC (BL = 74 ± 11%, FU = 68 ± 13%, $P = 0.01$) at 4-year follow-up. The baseline and 7-day short-term variability of VDP and pulmonary function measurements was previously reported (9). Briefly, no significant difference in spirometry or plethysmography were detected after 7 days but there was a difference in VDP (3 ± 4%, $P < 0.0001$) (9). In Fig. 2, $FEV1_1$, FVC, RV/TLC, and VDP are shown for all subjects and visits. At baseline, Subjects 2 and 4 presented with significantly worse VDP than the other three subjects (25% and 34%, respectively, $P = 0.02$), and these two subjects also showed significant VDP worsening at the longitudinal timepoint ($\Delta VDP = 0$ +17% and +11%, respectively, $P = 0.02$). In addition, for these two subjects (S2 and S4) there was an FEV_1 decline of 23% and 9%, respectively (mean $\Delta FEV_1 = -16 \pm 10\%$), while there was no change for Subjects 1, 3, and 5 (mean $\Delta FEV_1 = 0.3 \pm 1.5\%$). Exacerbations related to pulmonary CF disease showed that Subjects 2 and 4 both had a significantly greater frequency of annual exacerbations ($P < 0.05$; S2: 1.7/year and S4: 1.9/year) during the 4-year follow-up as compared to Subjects 1, 3, and 5 (0.4/year, 0.0/year, and 0.3/year, respectively). For Subjects 1, 3, and 5 there were no significant changes in VDP or FEV_1 between baseline and 4-year follow-up. For all subjects, as shown in Fig. 3, baseline VDP strongly correlated with FEV_1 after 4 years ($R^2 = 0.98$; $P = 0.0007$; 95% CI upper = –1.24, lower = –1.92). In addition, 4-year VDP was significantly strongly correlated with FEV_1 after 4 years ($R^2 = 0.85$, $P = 0.02$; 95% CI upper = –0.29, lower = –1.58).

Figure 4 shows ^{3}He MRI, MRI temporal difference maps, CT, and MRI-CT coregistered volumes for Subjects 2 and 4 at the 4-year timepoint. MRI temporal difference maps show increased ventilation abnormalities (in red) which were observed after 4 years in these two subjects. It is important to note that both subjects had CT evidence of multifocal traction bronchiectasis with peribronchial thickening and mucus plugging. Figure 4 shows the spatial relationship between ventilation defects and CT anatomical and morphological abnormalities consistent with bronchiectasis, inflammation, and mucus plugging. CT images show multifocal regions of bronchial dilation with thickening of the bronchial wall (yellow triangles) for airways in cross-section. Additionally, nontapering bronchiectatic airways in plane (red triangles) and areas of increased density suggestive of mucoid impaction or inflammation (purple triangles) are identified. These regional abnormalities are readily visualized in the MRI-CT coregistered volumes that identify the direct airway-pulmonary ventilation relationships at the 4-year timepoint.

DISCUSSION

Although lung disease is the major source of morbidity and mortality in CF, spirometry measurements of lung function only correlate weakly with long-term outcomes in CF patients (4). It is in this context that imaging measurements of CF pulmonary disease have been developed to help better understand those patients at risk of exacerbation and disease worsening. A previous study evaluated ^{3}He MRI ventilation measurement precision and short-term reproducibility in 12 CF subjects and significant changes in VDP were observed after 7 days that were not reflected by changes in spirometric or plethysmographic measurements (9). Here we evaluated the potential for longitudinal ^{3}He MRI ventilation measurements to identify, and better understand, CF patients with accelerated lung disease progression.

In this proof-of-concept demonstration, we longitudinally evaluated five young adults with CF and observed that ^{3}He MRI VDP was significantly worse at baseline for two CF subjects in whom VDP also

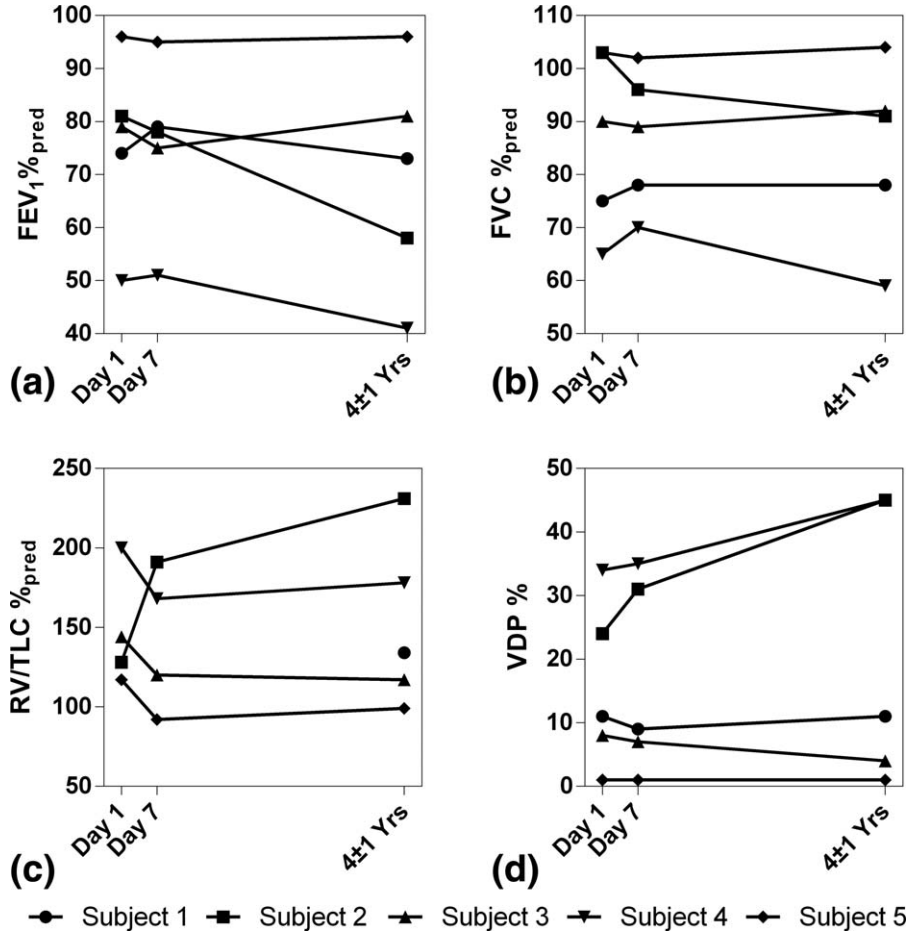

Figure 2. Pulmonary function and hyperpolarized ^{3}He MRI VDP measurements for all subjects and all study visits (Day 1: Baseline, Day 7: short-term follow-up, and 4 ± 1 years: long-term follow-up). (**A**) $FEV_1\%_{pred}$, (**B**) $FVC\%_{pred}$, (**C**) $RV/TLC\%_{pred}$, (**D**) ^{3}He MRI VDP.

worsened significantly over 4 years. For both patients, perhaps not surprisingly, these findings were in agreement with a greater number of exacerbations than the other three subjects. Recent work has shown that chest CT can be used in CF patients to identify regional disease changes and predict longitudinal FEV_1 declines (6). The potential for MR-based methods to help predict pulmonary function declines and assist in CF patient management decisions as shown in these cases is also encouraging. In Subjects 2 and 4, there was also CT evidence of extensive mucous plugging and multifocal traction bronchiectasis that was spatially correlated with ventilation abnormalities. The temporal ventilation variability maps also showed the direct spatial relationships of MRI functional changes with CT structural abnormalities. While the limited quantities of ^{3}He gas available preclude ^{3}He MRI clinical translation, these results suggest that functional MRI using other approaches such as oxygen-enhanced, ^{129}Xe, or ^{19}F may have the potential to provide valuable information in CF clinical trials and for clinical decision-making in CF patients.

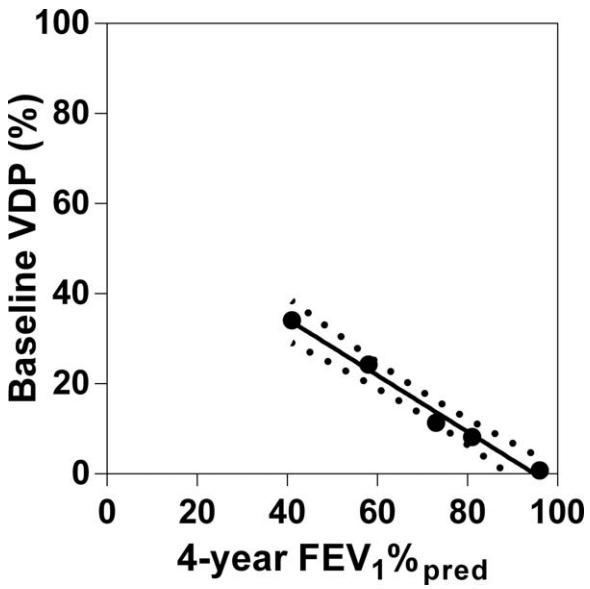

Figure 3. Relationship for VDP and FEV_1 for all subjects. FEV_1 after 4 years was strongly correlated with baseline VDP ($R^2 = 0.98$; $P = 0.0007$; 95% CI upper = –1.24, lower = –1.92).

While we were not surprised that patients with a greater frequency of exacerbations worsened significantly over 4 years, we did not anticipate that for all subjects in this small group baseline VDP was correlated with FEV_1 at 4-year follow-up. In previous work, a statistically significant relationship between FEV_1 and VDP was observed in 12 CF subjects (9). Not surprisingly, baseline FEV_1 was not correlated with VDP in this subset of five subjects. Interestingly, however, FEV_1 at 4 years correlated well with baseline VDP in

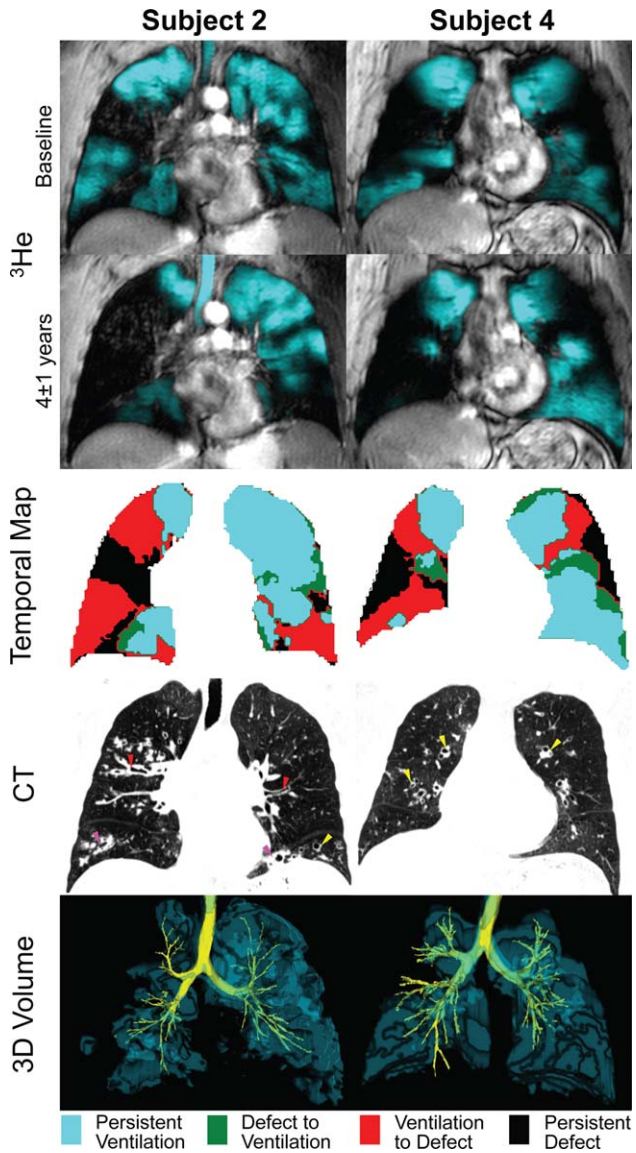

Figure 4. Coronal ^{3}He MRI at baseline and 4 years. Temporal MRI ventilation difference map, CT, and 3D ^{3}He MRI lung volume registered to CT-derived airway tree image for subjects S2 and S4. For the ^{3}He temporal ventilation difference map: black = persistent defect; cyan = persistent ventilation; red = ventilation to defect; green = defect to ventilation. For CT, triangles identify abnormalities spatially related to ventilation defects: yellow triangles identify bronchial dilation and thickening of the bronchial wall for airways in cross-section; red triangles identify in-plane nontapering bronchiectatic airways; purple triangles identify areas of increased density suggestive of mucoid impaction and/or inflammation.

this small group. In other words, when VDP was abnormal but still relatively low, the relationship with airflow obstruction was not strong, but once ventilation was highly abnormal (eg, >15%), FEV_1 abnormalities were measurable and there was a stronger correlation with VDP. This finding suggests that VDP might be predictive of CF progression and that abnormal VDP may precede FEV_1 declines. In this regard, it is interesting to note that for Subject 4 there was low FEV_1 at baseline (50%), and this is a strong predictor of risk of exacerbation and hospitalization (9). In contrast, for S2 who also experienced significant VDP worsening there was only mildly abnormal FEV_1 at baseline, suggesting milder disease burden, which was similar to Subjects 1, 3, and 5. This interesting finding raises the intriguing possibility that ^{3}He VDP may help stratify CF patients with mild airflow limitation but who require more careful monitoring to halt accelerated pulmonary disease progression. While it is also possible that VDP worsening precedes FEV_1 worsening in CF lung disease, it is important to interpret these findings with caution because of the small sample size. Accordingly, larger and likely multicenter longitudinal functional MRI studies in CF are needed to support these observations and to forge a better understanding of the relationships between ventilation measurements and progressive disease.

In addition to the small sample of CF subjects studied, we also must acknowledge that this study was limited to a single longitudinal visit and that by acquiring subject data on a more frequent basis there is the potential to measure changes in lung structure and function that can be directly attributed to specific events. A larger study in more subjects is required to confirm the utility of pulmonary functional MRI for monitoring CF, but the longitudinal changes measured here have the potential for earlier stage phenotyping that may influence patient management decisions. The scarcity and cost of ^{3}He gas should also be noted, as this certainly limits the feasibility of a larger CF study in the future. It is clear that hyperpolarized ^{3}He MRI will not be commercially or clinically translated and so MRI methods such as UTE-^{1}H-MRI, oxygen-enhanced MRI, or inhaled ^{19}F or hyperpolarized ^{129}Xe MRI will be required for ventilation imaging in CF patents in the future. It is also important to note that while all pulmonary function test values can be normalized for age, sex, size, and race, there are inadequate data in the literature to normalize VDP for this study. Hence, it is still difficult to clinically interpret VDP and its abnormalities in CF patients who are generally young never-smokers. However, recent work evaluating ventilation defects in healthy elderly never-smokers showed that mean VDP was $2.7 \pm 2.0\%$ (22). Based on these previous results, we can begin to develop an understanding of the clinical relevance of VDP in young CF subjects. This will certainly be required in order to interpret VDP changes over time and in response to therapy. Finally, underscoring the need for new radiation-free imaging measurements of CF, we must also point out that in our research and clinical environment, CT imaging is not often prescribed for CF patients because of the perception that the clinical benefit does not outweigh potential risks. This certainly limited the number of CT images that could be used here for structure–function comparisons.

While enormous progress has been made in the management of CF lung disease, new imaging tools have the potential to provide better objective and regional measurements of response to treatment and progressive disease worsening, with the goal of improving outcomes. In pediatric cases and young adults, functional MRI can be exploited serially and

longitudinally to safely and noninvasively monitor patients over long periods of time. The longitudinal pulmonary functional imaging results reported here have generated hypotheses to test related progressive worsening of pulmonary ventilation and other CF intermediate endpoints. These cases support the need for a larger prospective longitudinal study of CF using pulmonary functional MRI and emphasize the potential for MRI in CF clinical trials and drug discovery. We also believe that the measurements of pulmonary structure and function made safely and serially using MRI can be used to achieve the "holy grail" of CF therapy—novel treatments with disease-modifying activity (and not only FEV_1-modifying activity) that improve longitudinal outcomes. The findings here in five CF subjects suggest that ^{3}He MRI VDP may be a sensitive measurement of CF lung disease progression, and ventilation abnormalities measurable using MRI may temporally precede FEV_1 decline.

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