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Longitudinal Assessment of Children with Mild Cystic Fibrosis Using Hyperpolarized Gas Lung Magnetic Resonance Imaging and Lung Clearance Index

To the Editor:

With improving life expectancy in patients with cystic fibrosis (CF) and annual rates of decline in FEV_1 as low as 1–2% predicted per year (1), the value of spirometry as a measurement of longitudinal change is limited. Spirometry is also insensitive to early changes in the CF lung, and the lung clearance index (LCI) derived from multiple breath washout (MBW) has emerged as a promising alternative for patients with well-preserved spirometry, including children (2).

Recent studies have highlighted the potential of LCI for the longitudinal assessment of CF lung disease (3), although there are still questions regarding the mechanisms behind the mixed LCI response seen in intervention studies (4–6). As a global metric, however, LCI offers little information as to the location of any abnormality and the associated pathophysiology.

Hyperpolarized gas ventilation magnetic resonance imaging (ventilation MRI) is a sensitive imaging technique that reveals the distribution of ventilation within the lung in exquisite detail, allowing regional ventilation heterogeneity to be assessed. Ventilation MRI has been shown to be highly sensitive to early lung function abnormalities in CF and other obstructive airways diseases before changes are manifested in spirometry (7–9).

In a previous study, we reported cross-sectional data from a cohort of 19 children with mild CF lung disease (8). In that study, ventilation MRI demonstrated lung defects when abnormality was often not detectable by either computed tomography or LCI. Our aim in the present study was to reassess these children at a second time point 1–2 years after the baseline visit and describe any observed longitudinal changes in lung function or ventilation MRI. Some of the results of these studies have been previously reported in the form of abstracts (10–12).

Methods

Fourteen children with CF from the previously described cohort (8) were reassessed at a second time point between 1.3–2.0 years after baseline using helium-3 (^{3}He) ventilation MRI, MBW, spirometry, and body plethysmography as previously described (8). The patients were clinically stable (free from exacerbation and needing no new treatments) for at least 4 weeks before both visits and were on stable chronic medical regimens according to national guidelines. Two indices were calculated from the ventilation images: (*1*) the ventilation defect percentage (VDP), which quantifies the fraction of the lung volume that is not ventilated, and (*2*) the mean coefficient of variance of ventilated image signal intensity (CV_{mean}), which is a metric of ventilation heterogeneity.

The percentage change (Δ) from baseline to visit 2 was calculated for all metrics. The Wilcoxon matched-pairs signed-rank test and Spearman correlations were performed owing to the small sample size.

Table 1. Demographics, Lung Function, and Ventilation Imaging Metrics for Patients with Cystic Fibrosis at Baseline and Visit 2

	Baseline	Visit 2	*P* Value
Age, yr	10.30 (2.26)	12.07 (2.28)	<0.001
Height, cm	139.2 (13.89)	148.3 (12.88)	<0.001
Weight, kg	35.41 (13.26)	40.85 (12.42)	<0.001
FEV_1, *z*-score	−0.12 (0.80)	−0.26 (0.66)	0.349
FEV_1/FVC, *z*-score	−0.57 (0.65)	−0.47 (0.59)	0.903
RV/TLC, %	26.80 (4.58)	25.94 (4.38)	0.636
LCI	7.29 (0.85)	8.09 (1.44)	0.029
LCI_{supine}	7.64 (1.03)	8.77 (1.99)	0.042
S_{cond}	0.048 (0.025)	0.055 (0.029)	0.318
S_{acin}	0.132 (0.076)	0.129 (0.076)	0.985
VDP, %	4.37 (1.89)	10.8 (4.62)	<0.001
CV_{mean}, %	15.31 (2.30)	17.94 (3.33)	0.042

Definition of abbreviations: CV_{mean} = mean coefficient of variance of ventilated image signal intensity; LCI = lung clearance index; RV = residual volume; S_{acin} = ventilation heterogeneity arising from intraacinar airways; S_{cond} = ventilation heterogeneity arising from conducting airways; TLC = total lung capacity; VDP = ventilation defect percentage.
Data are mean (SD). *P* values from the Wilcoxon signed-rank test are given for baseline and visit 2 group comparison.

Supported by grants from the National Institute for Health Research (NIHR-RP-R3-12-027), Medical Research Council (MR/M008894/1), and Cystic Fibrosis Trust. L.S., A.H., and J.W. were supported by the NIHR, L.S. was supported by a Health Education England/NIHR clinical doctoral research fellowship, A.H. was supported by an NIHR Clinician Scientist award, and J.W. was supported by an NIHR Professorship award. The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health.

Author Contributions: Concept and design: J.W., C.J.T., and A.H. Analysis and interpretation: L.S., H.M., D.H., A.H., G.C., and J.W. Manuscript writing: L.S., H.M., A.H., and J.W. Manuscript review: all authors. Pulmonary function testing: L.S. MRI technical work: H.M., F.H., G.C., and J.W. Patient recruitment/consent/support: I.A., N.W., and C.J.T. Underwriting of the work: J.W.

Originally Published in Press as DOI: 10.1164/rccm.201705-0894LE on June 29, 2017

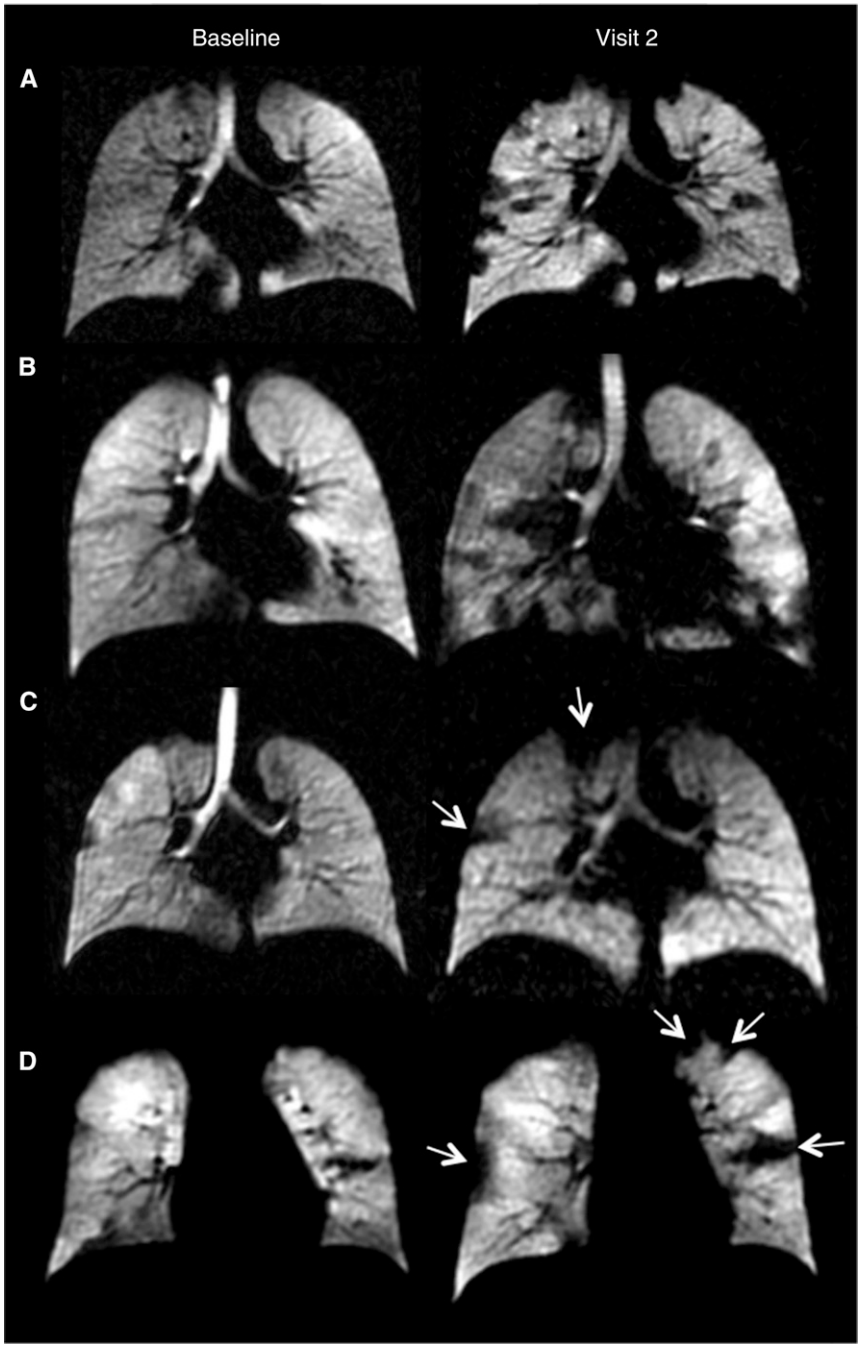

Figure 1. Representative ventilation magnetic resonance imaging slices from four separate subjects with cystic fibrosis. All four subjects had normal FEV_1 at both visits. Subjects *A* and *B* demonstrated widespread ventilatory defects visible at visit 2. The ventilation defect percentage (VDP) increased from 3.1% to 19.7%, the mean coefficient of variance of ventilated image signal intensity (CV_{mean}) increased from 15.9% to 20.1%, and the lung clearance index (LCI) increased from 6.6 to 8.7 for subject *A*. VDP increased from 3.4% to 19.4%, CV_{mean} increased from 11.9% to 24.5%, and LCI increased from 6.6 to 9.1 for subject *B*. Subjects *C* and *D* demonstrated localized ventilatory defects that largely increased in size from baseline to visit 2 (as shown by white arrows). VDP increased from 4.4% to 9.4%, CV_{mean} demonstrated a small decline from 15.2% to 14.9%, and LCI increased from 6.2 to 6.6 but remained well within the normal range for subject *C*. There was an increase in VDP from 7.5% to 10.3%, CV_{mean} from 13.3% to 16.6%, and LCI from 7.6 to 7.8 for subject *D*.

Results

Patient demographics, lung function, and MRI metrics at baseline and visit 2 are presented in Table 1. At baseline all children with CF had visible ventilation defects, and VDP and CV_{mean} were greater in CF patients compared with healthy controls, as reported previously (8). From baseline to visit 2, there were significant group increases in VDP, CV_{mean}, and LCI, but not in spirometric indices (Table 1).

Longitudinal changes in ventilation MRI. VDP increased over time in 13 of 14 children, and 10 of 14 children showed increased CV_{mean} at visit 2 compared with baseline. There was no single regional pattern of disease progression: in some patients, multiple small ventilation defects became apparent that were not visible at baseline (Figure 1, subjects A and B). Other patients had a visible progression in regions of ventilation abnormalities that were already present at baseline, but had minimal new defects (Figure 1, subjects C and D). One child showed improvement in VDP (and LCI) between baseline and visit 2, and the ventilation defects that were evident at baseline were either completely resolved or had reduced in size.

Longitudinal change in lung physiology. Six of 14 children had an abnormally elevated LCI (>7.4) at baseline. By visit 2, the LCI values had increased in 11 of 14, with eight children demonstrating abnormal LCI values. At baseline, all children had normal spirometry (FEV_1 and FEV_1/FVC z-score > -1.96) and only one child had an $FEV_1 < -1.64$. At visit 2, all children had an FEV_1 z-score > -1.64 and 13 of 14 children had an FEV_1/FVC z-score > -1.96.

Correlation between imaging and physiology. At both baseline and visit 2, there were statistically significant correlations between VDP and LCI ($r = 0.66$, $P = 0.013$, $r = 0.82$, $P = 0.001$, respectively), and a significant correlation between LCI and CV_{mean} was observed at visit 2 ($r = 0.62$, $P = 0.02$). There was no significant correlation between FEV_1 and FEV_1/FVC with either LCI or MRI metrics. ΔLCI showed significant strong correlations with ΔCV_{mean} ($r = 0.75$, $P = 0.003$) and ΔVDP ($r = 0.6$, $P = 0.025$). ΔFEV_1 and ΔFEV_1/FVC demonstrated no significant correlation with other metrics.

Discussion

With the current slow rate of decline in FEV_1 in stable CF lung disease, sensitive outcome measures of longitudinal changes in lung function are needed to guide therapy to maintain lung health. Ventilation MRI is capable of detecting significant lung function changes in the follow-up of children with CF and normal spirometry, which are not always evident using MBW. Although there was a significant group mean increase in LCI values between visits, highlighting the potential of LCI as a longitudinal assessment method, LCI was abnormal in only two more children at visit 2 (8/14) compared with baseline (6/14). However, ventilation MRI was abnormal in all children at both time points and showed increased ventilation impairment over time, as quantified by a highly significant increase in VDP. The nature of the changes in ventilation imaging varied between subjects, with new unventilated regions present at visit 2 in some patients and others showing an increase in the volume of unventilated regions, which were already present at baseline. The sensitivity of ventilation MRI to longitudinal therapy response in patients with CF has previously been demonstrated (13), but this is the first study to compare ventilation MRI and LCI for longitudinal assessment of lung disease progression in children with CF.

The observed improved sensitivity of ventilation MRI to longitudinal disease progression may be due to its ability to identify small changes within specific lung regions, in early disease, whereas LCI is a global assessment of lung function measured at a single point. In addition, unventilated regions of the lung will not contribute signal to outcomes that rely on gas mixing, causing an underestimate of measures such as the LCI.

In conclusion, although further data are still required, in children with CF and clinically stable lung function and normal spirometric values, hyperpolarized gas ventilation MRI appears to identify longitudinal changes in early lung disease earlier than other physiological methods. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Cardiovascular Disease Does Not Predict Exacerbation Rate or Mortality in Chronic Obstructive Pulmonary Disease

To the Editor:

Cardiovascular disease (CVD) is common in patients with chronic obstructive pulmonary disease (COPD) (1–4), yet it is unclear whether its presence increases the incidence of acute exacerbations (AECOPD) or the risk of death. Observational studies have shown that COPD is associated with a two to five times higher risk of ischemic heart disease (IHD), cardiac dysrhythmia, heart failure, diseases of the pulmonary circulation, and diseases of the arteries compared with non-COPD populations (4, 5). A prospective evaluation of COPD exacerbations in patients with comorbid IHD from the London COPD Cohort reported longer duration but not increased frequency of AECOPD in patients with IHD (6).

This prospective study was designed to test the hypothesis that the presence of CVD increases the risk AECOPD and/or death in patients with COPD recruited in a primary care setting.

Methods

The ACCESS (Assessment of Comorbidities in COPD in European Symptomatic Subjects) study (NCT01516528; GlaxoSmithKline study 115058) was a prospective, longitudinal, observational, nondrug interventional, 2-year study in patients with COPD enrolled from primary care in Belgium, France, Germany, the Netherlands, Poland, and Spain. Patients visiting their general practitioner for any reason were invited to participate if they were 40 years old or older, a current or ex-smoker (smoking history of $\geqslant$10 pack-years), had a minimum of 12 months of prior history of COPD, and had a FEV_1/FVC postbronchodilator ratio less than 0.70. Patients with a primary diagnosis of asthma, pulmonary fibrosis, asbestosis, any cancer, or clinically significant bronchiectasis were excluded.

Patients were followed up for 27 months through clinic visits at screening (−3 mo), baseline (0 mo), 12 months, and 24 months, and by phone at 3, 6, 9, 15, 18, and 21 months. Written informed consent was obtained from all subjects, and the study was approved by independent ethics committees as per the requirements in each country.

The prevalence of CVD at baseline was defined using a composite measure with previously published criteria (7). The primary outcome was the annual rate of moderate to severe AECOPD during the 24-month follow-up period. Moderate AECOPD was defined as a worsening of symptoms that required oral corticosteroids and/or antibiotics, whereas severe exacerbations were defined as those that included hospitalization. Mortality was a secondary outcome; details of patient deaths were obtained from the general practitioner.

To derive event rates and test associations, we applied multivariable negative binomial regression and Cox proportional hazards regression models, respectively. All analysis was prespecified except hospitalizations and mortality outcome modeling, which were *post hoc*.

Results

This analysis included 2,887 evaluable patients. Their mean age was 66 years, 70% were men, and 47% were current smokers with a mean postbronchodilator FEV_1% predicted of approximately 60% (Table 1). The mean number of moderate to severe AECOPD episodes in the previous year was 0.61 (95% confidence interval [CI], 0.57–0.64); for severe AECOPD, it was 0.08 (95% CI, 0.07–0.09). At baseline, patients with COPD with CVD (1,375; 48%) were older and more likely to be ex-smokers but had a similar airflow limitation and history of exacerbations to those without CVD.

Over the course of 24 months, there was no difference in the annualized rate of AECOPD between those with or without CVD (adjusted rate per patient, 0.63 [95% CI, 0.57–0.69] vs. 0.63 [95% CI, 0.58–0.69]; rate ratio, 0.99 [95% CI, 0.88–1.11]; Table 2). Male sex, lower postbronchodilator FEV_1% predicted, and higher COPD Assessment Test score, but not older age, were significantly independently associated with a higher overall rate of exacerbations. Addition of history of AECOPD events in the 12 months before study baseline into models was significantly

This study was funded by GlaxoSmithKline.

Author Contributions: All authors contributed to the study design and conduct, interpreted the results, and participated in the manuscript writing. H.M., L.A., A.R., and C.-Q.Z. also contributed to the study data analysis plan.

Originally Published in Press as DOI: 10.1164/rccm.201706-1066LE on June 30, 2017