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Longitudinal assessment of children with mild CF using hyperpolarised gas lung MRI and LCI

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Introduction

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

Recently the potential of LCI in the longitudinal assessment of CF lung disease has been highlighted (3), though there are still questions with regards to 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.

Hyperpolarised 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).

We have previously reported cross-sectional data on a cohort of 19 children with mild CF lung disease where ventilation MRI demonstrated lung defects when abnormality was often not detectable on either CT or LCI (8). The aim of the present study was to re-assess these children at a second time point 1-2 years

following 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

14 children with CF from the cohort previously reported (8) were re-assessed 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 using the same methods as previously described (8). Patients were clinically stable for at least 4 weeks prior to both visits (free from exacerbation and needing no new treatments) and were on stable chronic medical regimens according to national guidelines. From the ventilation images two indices were calculated; (i) the ventilation defect percentage (VDP), which quantifies the fraction of the lung volume that is not ventilated, and (ii) the mean co-efficient of variance of ventilated image signal intensity (CV_{mean}), a metric of ventilation heterogeneity.

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

Results

Patient demographics, lung function and MRI metrics at baseline and visit two 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 than healthy controls (as reported previously (8)). From baseline to visit two 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 13/14 children, whilst 10/14 children showed increased CV_{mean} at visit two compared to baseline. There was no single 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 two: in this individual the ventilation defects evident at baseline were either completely resolved or had reduced in size.

Longitudinal change in lung physiology

6/14 children had an abnormally elevated LCI (>7.4) at baseline. By visit two, LCI values had increased in 11/14, 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 two all children had an FEV_1 z score >-1.64 and 13/14 children had an FEV_1/FVC z-score >-1.96.

Correlation between imaging and physiology

At both baseline and visit two 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 two (r=0.62, p=0.02). There was no significant correlation between FEV_1 and FEV_1/FVC with 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 change 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 is not always demonstrable 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 two (8/14) compared to baseline (6/14). Ventilation MRI however was abnormal in all children at both time-points, and showed increased ventilation heterogeneity over time, quantified by a highly significant increase in VDP. The nature of increased ventilation heterogeneity varied between subjects, with new unventilated regions present at visit two 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 changes within lung regions, which tend to be small in early disease, whilst 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 relying on gas mixing, causing an underestimate of measures such as LCI.

In conclusion, whilst further data is still required, in children with CF and clinically stable lung function and normal spirometric values, hyperpolarised gas ventilation MRI appears to identify longitudinal changes in early lung disease prior to other physiological methods of early lung disease detection.

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Table 1: Mean (standard deviation) CF patient demographics, lung function and ventilation imaging metrics at baseline and visit 2. P-values from Wilcoxon signed-ranks test are given for baseline and visit 2 group comparison.

	Baseline	Visit 2	P-value
Age (years)	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

Figure 1: Representative ventilation MRI slices from four separate CF subjects. All four subjects had normal FEV_1 at both visits. Subjects A and B demonstrated widespread ventilatory defects visible at visit two. VDP increased from 3.1% to 19.7%, CV_{mean} from 15.9% to 20.1% and LCI from 6.6 to 8.7 for subject A. VDP increased from 3.4% to 19.4%, CV_{mean} from 11.9% to 24.5% and LCI from 6.6 to 9.1 for subject B. Subjects C and D demonstrated localised ventilatory defects that largely increased in size from baseline to visit two (as shown by white arrows). VDP increased from 4.4% to 9.4%, yet CV_{mean} demonstrated a small decline from 15.2% to 14.9%, LCI increased from 6.2 to 6.6 but remains well within the normal range for subject C. VDP increased 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.

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