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The assessment of short and long term changes in lung function in CF using ^{129}Xe MRI

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Take Home Message: ^{129}Xe-MRI in CF is highly repeatable. In patients with normal FEV_1, ^{129}Xe-MRI is also sensitive to detect changes in longitudinal lung function and should be highly informative in an era of CFTR modulators and increasingly preserved FEV_1

Abstract

Introduction: ^{129}Xe ventilation MRI is sensitive to detect early CF lung disease and response to treatment. ^{129}Xe-MRI could play a significant role in clinical trials and patient management. Here we present data on the repeatability of imaging measurements and their sensitivity to longitudinal change.

Methods: 29 children and adults with CF and a range of disease severity were assessed twice, a median [IQR] of 16.0 [14.4,19.5] months apart. Patients performed ^{129}Xe-MRI, lung clearance index (LCI), body plethysmography and spirometry at both visits. Eleven patients repeated ^{129}Xe-MRI in the same session to assess the within-visit repeatability. The ventilation defect percentage (VDP) was the primary metric calculated from ^{129}Xe-MRI.

Results: At baseline, mean (SD) age = 23.0 (11.1)years and FEV_1 z-score = -2.2 (2.0). Median [IQR] VDP = 9.5 [3.4,31.6]%, LCI = 9.0 [7.7,13.7]. Within-visit and inter-visit repeatability of VDP was high. At 16 months there was no single trend of ^{129}Xe-MRI disease progression. Visible ^{129}Xe-MRI ventilation changes were common, which reflected changes in VDP. Based on the within-visit repeatability, a significant short-term change in VDP is >±1.6%. For longer-term follow up, changes in VDP of up to ±7.7% can be expected, or ±4.1% for patients with normal FEV_1. No patient had a significant change in FEV_1, however 59% had change in VDP >±1.6%. In patients with normal FEV_1, there were significant changes in ventilation and in VDP.

Conclusions: ^{129}Xe-MRI is a highly effective method for assessing longitudinal lung disease in patients with CF. VDP has great potential as a sensitive clinical outcome measure of lung function and endpoint for clinical trials.

Introduction

For people with cystic fibrosis (CF), advances in treatments and patient management have significantly increased expected survival. These advances have greatly improved the lung health of patients and now the median FEV_1 for UK patients <18 years is well preserved at 88% predicted[1]. It is however also well accepted that a value for FEV_1 within the range of normal does not necessarily mean that the patient's lung function is truly normal[2, 3]. With highly effective CFTR modulator therapies being increasingly administered to patients with an FEV_1 within the normal range, more sensitive outcome methods for assessing lung function are therefore required.

Hyperpolarised gas ventilation MRI using either helium-3 (^{3}He) or xenon-129 (^{129}Xe) provides a direct visual and quantitative assessment of the distribution of ventilation within the lung in 3D [4]. Ventilation abnormalities are clearly identified as areas of signal deficit and are termed ventilation defects. The ventilation heterogeneity seen on MRI can be quantified using different approaches to assess the degree of abnormality. The metric most widely used is the ventilation defect percentage (VDP), which quantifies the proportion of the image without any ventilation present. A major strength of ventilation MRI is the ability to measure individual ventilation defects, which allows for small regional changes in lung function to be assessed[5].

Previous studies in CF populations using ^{3}He showed that ventilation MRI is highly sensitive to detect early lung disease in subjects with normal values for FEV_1[6-12], lung clearance index (LCI)[5, 6] and CT imaging[6]. The latter two methods are already recognised as sensitive methods for the detection of early lung disease[3, 13]. Previously, a study of young patients with mild CF lung disease showed that ^{3}He MRI was sensitive to longitudinal changes in lung function that were largely undetected by FEV_1 and LCI[14]. In more recent years, ventilation MRI research has moved from ^{3}He towards ^{129}Xe due to the lower cost and greater availability of ^{129}Xe. Recent studies utilising ^{129}Xe MRI in CF have found that it is well tolerated[15] and is also sensitive to detect early lung disease[16, 17]. ^{129}Xe MRI has also been shown to be sensitive to treatment response to pulmonary exacerbation in children with CF, with ^{129}Xe VDP showing a larger treatment response than both LCI and FEV_1[18].

Hyperpolarised gas ventilation MRI is therefore an attractive method for assessing CF lung disease, but more data are required on the background longitudinal changes seen in stable CF lung disease. This includes a systematic assessment of the intrinsic technical repeatability of the measurement in this population, which preliminary data suggests is promising[19], as well as the pathophysiological variability seen in stable disease. Therefore, in this study we aimed to assess the potential of ^{129}Xe MRI as a quantitative outcome measure of lung health and a possible candidate endpoint for clinical trials

and patient management. In order to do this we assessed the short and long term repeatability of imaging (VDP) in a cohort of children and adults with CF and a range of lung disease. We also aimed to better understand the longitudinal changes in lung function on ^{129}Xe MRI in comparison to LCI and FEV_1 in those patients with an FEV_1 within the normal range.

Methods

This prospective study recruited adults and children (>5 years old) with CF from three specialist CF centres in the UK (Sheffield Children's Hospital and Northern General Hospital, Sheffield, UK and Manchester Adult CF Centre, Manchester, UK). For inclusion, patients had to be clinically stable for four weeks prior to assessment (defined as free from intravenous antibiotics or any hospital stay within 4 weeks) and have an FEV_1 >30% predicted within the previous 6 months. This study was approved by the Yorkshire and Humber - Leeds West Research Ethics Committee (REC reference: 16/YH/0339). Parents/guardians of children and all adult patients provided written informed consent.

Lung imaging

Hyperpolarised ^{129}Xe ventilation MRI of the lungs was performed at a single site (Sheffield) on a 1.5T GE HDx scanner (GE Milwaukee, USA) using previously described protocols[20]. Xenon-129 was polarized using bespoke spin exchange optical pumping polarizer[21], under a UK MHRA manufacturing specials regulatory licence (MS-18739). Ventilation imaging was acquired at a lung volume of end-inspiratory tidal volume (EIVt), by inhaling a volume of ^{129}Xe titrated with a balance of medical-grade nitrogen, from a lung volume of functional residual capacity. The total inhaled gas volume ranged from 0.4-1.0L and was calculated based on the subject's height. For ^{129}Xe analysis a ^{1}H anatomical image was performed in a separate breath-hold (immediately prior to the ^{129}Xe image) in order to calculate the thoracic cavity volume (TCV). For quantitative analysis, the ^{1}H and ventilation images were segmented using a semi-automated method[22], from which the ventilation defect percentage (VDP) and the ventilation heterogeneity index (VH_I), which reflects the heterogeneity of ventilated voxels within ventilated lung regions, were calculated as previously described[5]. Further details of image acquisition and processing methods can be found in the OLS.

In order to assess the within-visit technical repeatability of ^{129}Xe-MRI, ^{129}Xe imaging was repeated in a sub-group of patients within 15 minutes of the initial baseline measurement and without the subject leaving the scanner. The same imaging protocol, respiratory manoeuvres and volume of gas were used for both scans.

Lung physiology

Patients performed multiple-breath washout on the same day and at the same centre as imaging using an open-circuit Innocor gas analyser (Pulmotrace, Glamsberg, Denmark) using 0.2% SF_6[23]. LCI was calculated from the average of three trials as recommended[24]. Body plethysmography was performed using a 'PFT Pro' (Vyaire, Basingstoke, UK) according to guidelines[25], in order to calculate the ratio of residual volume (RV) to total lung capacity (TLC). Finally, spirometry was performed according to guidelines[26] and expressed as z-scores[27]. Either MRI or LCI was performed first, followed by the other. Spirometry was always performed last.

The assessments of ^{129}Xe ventilation MRI, MBW and spirometry were then repeated at a second stable visit using the same methods described.

Statistical analysis

Data were analysed using Prism version 8.0 (GraphPad, San Diego, USA) and SPSS statistics version 26.0 (IBM, New York, USA). Normal distribution was assessed using the Shapiro-Wilk test. Data are expressed as mean (SD) for normally distributed data, and median [IQR] for non-parametric data. Within-visit repeatability of ^{129}Xe-MRI was assessed from the 95% limits of agreement (LOA) of a Bland-Altman analysis of the repeat measurements. Wilcoxon signed-rank test and Bland-Altman analysis were used to compare MRI and lung function metrics between the baseline and follow-up study visits. Within-visit and inter-visit repeatability was calculated using the intra-class correlation coefficient (ICC). Spearman correlation analysis was used to compare the change in different metrics. Sample size power calculations were calculated for different effect sizes based on the longitudinal data[28]. Statistical significance was set at $p<0.05$.

In order to assess whether a clinically significant change in VDP had occurred over time, firstly the Bland-Altman LoA from the within-visit repeatability measurements was used as a minimal threshold. Secondly, a further threshold to represent a clinically significant change in absolute VDP was set at ±3%; this threshold represents the mean absolute change in ^{129}Xe VDP in response to treatment of an exacerbation of CF lung disease[18]. In order to compare the significance of change in VDP, similar thresholds for short and long term repeatability were applied for LCI and FEV_1. Repeatability of ±10% in LCI has been shown for healthy volunteers[23], whilst longitudinal changes of ±20% have been reported in clinically stable CF patients[29]. For FEV_1, a within-patient longitudinal change of >±10% is deemed significant[30], whilst the short-term change of FEV_1 in patients with CF is approximately ±5%[31, 32].

Results

Twenty nine children and adults with CF were assessed on two occasions, a median of 16 months apart. At baseline, patients were aged between 6 and 47 years. Baseline demographics, MRI metrics and lung function are detailed in Table 1. All but one patient had visible ventilation defects present at both study visits. Fourteen patients (48%) had a normal FEV_1 value (>-1.64 z-score) at both baseline and follow up. Three patients (10%) at baseline, and seven (24%) at follow-up had normal LCI values.

Table 1: Patient demographics, ^{129}Xe MRI and pulmonary function metrics are displayed as Mean (SD) or median [IQR] at both study visits.

	Baseline visit	**Follow up visit**	**Absolute change** (Δ)	**Relative change** (%)	**ICC** {95% C.I.}	**Bland Altman** Bias {LoA}
Demographics						
No. of patients (% female)	29 (52)					
Age (years)	23.0 (11.1)	24.3 (11.1)				
Height (cm)	160.3 (16.2)	162.9 (14.3)				
Weight (kg)	54.7 (17.4)	56.6 (17.0)				
^{129}Xe MRI						
VDP (%)	9.5 [3.4, 31.6]	10.5 [3.0, 29.4]	0.5 [-1.8, 2.4]	8.2 [-13.9, 35.5]	0.97 {0.94, 0.99}	0.8 {-7.0, 8.5}
VH_I (%)	14.2 [10.3, 17.7]	12.6 [9.7, 18.3]	-0.1 [-0.9, 1.1]	-1.1 [-7.1, 11.0]	0.89 {0.80, 0.95}	0.3 {-3.7, 4.3}
Pulmonary function						
FEV_1 (z-score)	-2.2 (2.0)	-2.3 (2.0)	-0.0 (0.4)	0.2 [-14.5, 12.0]	0.98 {0.96, 0.99}	-0.1 {-0.8, 0.7}
FEV1 (% predicted)	72.1 (25.6)	71.3 (25.5)	-0.8 (5.0)	-1.1 (7.9)	0.98 {0.96, 0.99}	-0.8 {-10.5, 8.9}
LCI	9.0 [7.7, 13.7]	8.9 [7.5, 14.5]	0.3 [-0.9, 1.1]	4.3 [-7.9, 10.2]	0.95 {0.90, 0.98}	0.3 {-2.2, 2.8}
RV/TLC (%)	35.3 [26.0, 47.1]	34.4 [25.3, 48.7]	0.0 [-2.5, 2.7]	0.0 [-6.4, 7.9]	0.96 {0.91, 0.98}	0.1 {-7.3, 7.6}

The absolute change refers to the difference of follow up – baseline as does the Bland-Altman data. The relative change is the percentage change from baseline. The ICC is the Intra-class correlation coefficient between the two time points and is displayed with the 95% confidence intervals (C.I.). Bland-Altman data is displayed as the bias {95% limits of agreement (LoA)}. VDP = ventilation defect percentage. VH_I = ventilation heterogeneity index. FEV_1 = forced expiratory volume in 1 second. LCI = lung clearance index. RV/TLC = the ratio of residual volume to total lung capacity.

Within-visit repeatability of ^{129}Xe

Eleven patients (35%) performed repeat ^{129}Xe-MRI within 15 minutes of the baseline scan. Median [IQR] age = 23.7 years [17.7, 33.2], baseline VDP = 7.3% [2.5, 30.8], LCI = 8.3 [7.3, 14.0], FEV_1 = -2.4 z-score [-2.8, -0.5]. There was no significant difference in VDP between scans and good repeatability with a bias of 0.2% and 95% LoA = -1.4,1.8%. This represents the intrinsic technical repeatability of the measurement *in vivo* assuming no true change in underlying lung ventilation. Based on this analysis a threshold of absolute change in VDP of ±1.6% was used in part to assess ^{129}Xe VDP longitudinal change. Repeatability for VH_I can be found in Figure 5, alongside the Bland-Altman plots for VDP. For VH_I, there was again minimal bias (-0.6), with 95% LoA = -2.5, 1.2%. The within-visit ICC for VDP was excellent at 0.99 (95% CI = 0.99, 1.0) and for VH_I = 0.96 (95% CI = 0.84, 0.99).

Longitudinal change in ^{129}Xe MRI

All 29 patients successfully repeated ^{129}Xe MRI and lung function testing at a second visit, after a median [IQR] interval of 16.0 [14.4, 19.5] months. There was no single pattern of disease progression in the cohort and no lung function or MRI metric demonstrated a statistically significant group change between visits. Instead, significant inter-subject variation was seen in the degree and direction of change in ventilation distribution on ^{129}Xe MRI. For many patients there were clear and often large visible changes in the distribution of ventilation, independent of underlying disease severity (Figures 1, 2 and 3). Figure 1 shows eight example images from patients, all of whom had normal-range FEV_1, where there was a change in the distribution of ventilation and in VDP, but without significant change in FEV_1 or LCI (see also Figures 2 and 3).

Longitudinal change relative to baseline for VDP, LCI and FEV_1 are shown in Figure 4. Overall, 17 patients (59%) had an increase (worsening) in VDP at follow up, which correlated with the visual image analysis (Figures 4 and 5). Seventeen patients (59%) had a change in ^{129}Xe VDP of >±1.6%, whilst nine (31%) also had an absolute change in VDP >±3%. In comparison, 13 (45%) had a relative change in LCI >10% from baseline, but only 2 (7%) had a relative change greater than ±20%. For FEV_1, 10 (34%) had an absolute change in FEV_1 %predicted of >±5% and no patients had an absolute change >±10%. Of the 9 patients with a change in VDP >±3%, no patient had a corresponding significant change in LCI or FEV_1. Of all the metrics, ^{129}Xe VDP had the highest median relative change over time (8.2%).

Inter-visit repeatability

The inter-visit ICC for ^{129}Xe VDP was excellent at 0.97, which was similar to FEV_1 (0.98) and higher than LCI (0.95), RV/TLC (0.96) and ^{129}Xe VH_I (0.89) (Table 1). The change in VDP tended to be larger for those with higher baseline VDP. When only patients with normal FEV_1 were considered (and therefore with lower values for VDP) the 95% LoA fell from -6.9 to 8.5% for the whole cohort to -4.3 to 4.0% (n=14) (Figure 5).

Correlation of the changes in metrics over time

The absolute or relative change in VDP was not correlated with absolute or relative change in FEV_1, LCI or RV/TLC. In contrast the absolute and the relative changes in VH_I and LCI were significantly correlated with each other ($r=0.68$, $p<0.001$ and $r=0.73$, $p<0.001$ respectively). There was no correlation in the change in either FEV_1 or RV/TLC with the other metrics. There was also no relationship between the magnitude of change in VDP with age or underlying lung disease as measured at baseline.

Sample size power calculations

With a view to using VDP from ^{129}Xe MRI as an intervention outcome marker, sample size calculations for four different effect sizes and three populations were derived. Effect sizes include the minimal change of 1.6% in VDP, the mean change of 3% seen with intravenous antibiotics, and 5 and 10% change. Population mean and SD are taken from the whole cohort data (representing a mixed CF population with a wide range of disease severity) and, separately, only those with normal-range FEV_1. The results are presented in Table 2. This emphasises the importance of the baseline variability and appropriate population selection, but also shows the low numbers that are potentially required to detect significant change. For example a 3% change could be detected with a power of 90% in a study population of 11 patients with CF and normal FEV_1.

Table 2: Sample size power calculations for different effect sizes, based on ^{129}Xe VDP and different patient populations.

			Effect size							
			1.6%		**3%**		**5%**		**10%**	
P=	**N=**	**S.D. of ΔVDP**	**80%**	**90%**	**80%**	**90%**	**80%**	**90%**	**80%**	**90%**
1. Sub-group, within-visit repeatability	11	0.82	5	6	2	2	1	1	1	1
2. Whole CF cohort, longitudinal repeatability	29	3.93	95	127	27	37	10	13	3	4
3. CF cohort with normal FEV_1, longitudinal repeatability	14	2.11	28	37	8	11	3	4	1	1

Population 1 is patients who underwent same-day ^{129}Xe repeatability scans. Population 2 is the complete cohort with two ^{129}Xe images approximately 16 months apart and population 3 is the same cohort, but with only those included who had normal FEV_1. P = population number. N = number of patients measured. S.D. of ΔVDP = the standard deviation of the difference in VDP between two time-points.

Discussion

The data reported in this study are the first longitudinal assessment of patients with CF using ^{129}Xe lung ventilation MRI. In this study we demonstrate that i) ^{129}Xe MRI VDP has high within-visit repeatability; ii) that a qualitative and quantitative approach to image analysis is complementary in assessing CF lung disease; and iii) that in patients with a preserved FEV_1, as well as those with more advanced disease, VDP demonstrates changes in ventilation distribution in patients where FEV_1 and LCI do not show significant change.

There is a growing body of evidence that ventilation MRI provides valuable and detailed insights into the underlying lung function of patients with CF that is not detected by other methods[5-12, 14, 16-18, 33]. Previous studies have shown that ventilation MRI is highly sensitive to early lung disease and in the case of ^{3}He, is repeatable[34, 35] and sensitive to disease progression[14]. The data presented in this study adds to this evidence base by demonstrating that ^{129}Xe MRI is also highly sensitive to detect longitudinal changes in CF lung disease. Unlike the previous study from our group[14], performed in children with mild CF lung disease using ^{3}He MRI, here we did not see one single pattern of disease progression. Of the cohort reported here, 59% of patients had evidence of increase in VDP, whilst the remaining patients showed improvements in ventilation. This is not surprising given that this is a broad cohort of patients, in terms of age and disease severity, although there was no relationship between the magnitude of change in VDP with either age or disease severity. Ventilation defects caused by mucus obstruction will not necessarily remain stable. Thus some visible defects will represent short term reversible obstructions whilst others may be caused by underlying disease progression and airway narrowing. Figure 1 shows how in patients with normal FEV_1, ^{129}Xe MRI is able to detect early disease-related changes, as we previously reported with ^{3}He MRI. Figure 1 also shows that changes in lung ventilation can be measured on ^{129}Xe MRI that are not necessarily detected by LCI. This is a particularly important finding in the era of new and expensive CFTR-modulating therapies, where there is a need to be able to measure clinical response to therapies even in those with apparently normal lung function. ^{129}Xe MRI VDP is a metric that may provide this detail, as has previously been shown for ^{3}He MRI in the assessment of Ivacaftor[33]. In addition, there is also increasing evidence for the application of ^{1}H structural MRI in the clinical assessment of CF lung disease[36-39]. ^{1}H MRI can be performed at the same visit as ^{129}Xe MRI, allowing for the combined assessment of lung structure and function when measured together.

Inter-visit repeatability is affected by sources of both intrinsic (technical) and physiological variability, as well as true disease progression. For VDP, a change of >±1.6% is greater than the inter-subject intrinsic repeatability of the measurement, and potentially represents a lower threshold for significant

change. For comparison, a median change of >±3% in VDP in response to IV antibiotics should represent a clinically significant degree of change[18]. The true threshold for clinically relevant change in VDP therefore likely lies between these limits, but cannot be more precisely determined from the data available. Over longer time courses however, CF patients have natural fluctuations in mucus plugging and symptoms, which are separate from underlying disease progression. We have shown that over 16 months, a change in VDP of up to ±7.7% is seen in CF patients considered to be clinically stable and without obvious disease progression by other lung function metrics; the change is less (at ±4.1%) in those with a preserved FEV_1.

The findings that lung function metrics on average are unchanged with time are consistent with longitudinal analyses of patients with CF using LCI, where minimal longitudinal change was reported[40-43]. Our findings, in addition, highlight that patients with CF are as likely to clinically improve as they are to have deteriorating ventilation heterogeneity during observational follow up. Despite this, Figures 1, 3, 4 and 5 show that patients often had sub-clinical changes in VDP without significant change in FEV_1 or LCI. It is likely that some of these changes we have seen in ventilation are transient and some are the precursor to exacerbation and potentially irreversible ventilation changes.

In this study we highlight how VDP can sensitively track changes in underlying lung function in patients with preserved FEV_1, which correspond to visual changes on the ventilation images (See Figures 1 and 2). In order to assess this specific patient population in clinical trials, relatively large sample sizes are required to measure modest treatment effects when FEV_1 is the primary outcome[44]. LCI has been used as an alternative outcome in more recent studies[45], which allows for smaller sample sizes in patients with normal FEV_1. ^{129}Xe VDP however has high repeatability, low SD and large effect sizes can be measured, which is reflected in the relatively small sample sizes required to measure the different reported effect sizes.

^{129}Xe VDP is an attractive potential outcome measure / endpoint in both clinical trials and clinical management. A strength of ^{129}Xe MRI is that not only can we produce summary whole-lungs metrics like VDP that are more sensitive than LCI and FEV_1 at detecting early lung disease, but the images themselves also contain more detailed regional functional information[5]. It is possible therefore to detect clinically relevant regional change even in the face of apparently unchanged lung physiology tests[5, 46]. This applies both to detecting disease progression in clinical practice over time courses like the one described in this study, as well as detecting much shorter-term improvements due to therapeutic interventions[18, 33]. In order to generate quantitative regional metrics of lung physiology from ventilation MRI, future work should focus on reliable parameterisation of regional ventilation heterogeneity to further improve the clinical utility of ventilation MRI.

We recognise that hyperpolarised gas ventilation MRI is not currently available to many CF centres. Estimates of regional lung function may also be acquired indirectly, without the use of inhaled contrast agents using time-resolved ^{1}H MRI techniques[47, 48] or by using contrast enhanced perfusion MRI[38]. These techniques are promising and may provide an alternative, more widely accessible method to the wider CF community. A further limitation of this study is the lack of detailed clinical data to cover the period between visits, which may have helped explain some of the changes seen. We also acknowledge that this is a single-centre analysis, which may have an impact on the data, however a recent study reported the high repeatability of ^{129}Xe VDP in a multi-centre setting[49], which highlights the potential of VDP as an endpoint in multi-centre studies.

In conclusion, ^{129}Xe MRI is a highly effective method for the assessment of CF lung disease. In this study, ^{129}Xe VDP has high within-visit repeatability and measures underlying changes in lung function that are not necessarily detected by other methods. Measuring small changes in lung function in a patient population with increasingly normal, preserved spirometry values, is challenging but highly relevant. ^{129}Xe ventilation MRI can both qualitatively and quantitatively meet this requirement and should therefore be considered as a future endpoint for clinical trials and patient management.

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