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THE EFFECT OF ACUTE MAXIMAL EXERCISE ON THE REGIONAL DISTRIBUTION OF VENTILATION USING VENTILATION MRI IN CF

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Abstract

Background: The importance of exercise in the management of people with CF is well recognised, yet the effect of exercise on lung function is not well understood. FEV₁ is insensitive to the detection of small changes in lung function. Ventilation MRI and LCI are both more sensitive to mild lung disease than FEV₁ and may be better suited to assess the effects of exercise. Here we assessed the short-term effects of maximal exercise on the distribution of ventilation using ventilation MRI and LCI.

Methods: Patients with CF and a range of lung disease were assessed. Baseline LCI and ventilation MRI was followed by a maximal cardio-pulmonary exercise test (CPET). Repeated ventilation MRI was performed within 30 minutes of exercise termination, followed by LCI and finally by FEV₁.

Results: 13 patients were recruited and completed all assessments. Mean (SD) age was 25 (10) years and mean (SD) FEV₁ z-score was -1.8 (1.7). Mean LCI at baseline was 8.2, mean ventilation defect percentage on MRI (VDP) was 7.3%. All patients performed maximal CPET. Post-exercise, there was a visible change in lung ventilation in 85% of patients, including two patients with increased ventilation heterogeneity post-CPET who had normal FEV₁. VDP and LCI were significantly reduced post-exercise (p<0.05) and 45% of patients had a significant change in VDP.

Conclusions: Acute maximal exercise directly affects the distribution of ventilation on ventilation MRI in patients with CF. This suggests that exercise is beneficial in CF and that ventilation MRI is suitable to assess airway clearance efficacy.

Non-standard abbreviations:

¹²⁹Xe – Xenon-129

³He – Helium-3

LCI – Lung Clearance Index

MBW – Multiple Breath Washout

VDP – Ventilation Defect Percentage

VH₁ – Ventilation Heterogeneity Index

1.1 Introduction

Exercise is increasingly recognised as an important component of disease management in cystic fibrosis (CF)(1). Aerobic capacity, in particular the amount of oxygen uptake during maximal exercise ($VO_2\text{peak}$), is highly predictive of long-term morbidity and mortality(2-4). $VO_2\text{peak}$ and other metrics calculated from lab-based cardio-pulmonary exercise testing (CPET) such as the ventilatory equivalents for O_2 and CO_2 (Ve/VO_2 and Ve/VCO_2 respectively), are strong predictors of hospitalisation(5), death and lung transplantation(4). As a result, there is increasing emphasis on performing routine lab-based CPET assessments in CF because of the detailed physiological profiling the interpretation can provide(6).

There is also recognition in the value of exercise as a form of chest physiotherapy(7). The increased minute ventilation associated with exercise, as well as the upper body movement that often accompanies exercise, causes increases in positive pressure within the lungs, which aids the clearance of mucus from airways(7). Many patients with CF use exercise as a primary form of physiotherapy(1) and the role of exercise in airway clearance has been highlighted as one of the most important questions that people with CF are interested in(8). Previous studies have demonstrated that maximal exercise causes an improvement in the lung clearance index (LCI)(9) measured during a multiple breath washout (MBW) test, suggesting ventilation heterogeneity is improved as a result of exercise. In contrast however, attempts at measuring long-term improvements in lung function due to regular exercise have not demonstrated significant changes in FEV_1 (10). FEV_1 however is not a sensitive enough metric to monitor the effects of chest physiotherapy in general(11).

Hyperpolarised gas ventilation MRI using helium-3 (^3He) or, increasingly, xenon-129 (^{129}Xe) provides a direct visualisation in 3D of the distribution of ventilation within the lung. Ventilation MRI has been shown to be highly sensitive to early lung disease in CF(12) and to longitudinal disease progression(13). Ventilation MRI has also been shown to be effective at measuring the effect of interventions, including CFTR modulators(14) and antibiotics in response to acute exacerbation(15). A major strength of ventilation MRI, is the ability to quantitatively assess global and regional lung disease(16), with the ventilation defect percentage (VDP) being the most common metric reported. Previous studies have assessed the effect of chest physiotherapy using ^3He MRI, and shown that physiotherapy causes a re-distribution of ventilation that can

be imaged and quantified(17-19). In addition to the detection of changes in regional ventilation, due to shifting mucus distribution, it might also be anticipated that the severity of ventilation abnormalities observed on MRI would be related to the degree of exercise impairment in people with CF. Ventilation MRI is thus a well-placed tool to assess both the impact of airway disease on exercise capacity, and the impact of exercise on lung physiology.

In this work we hypothesised that a period of maximal exercise would result in airway clearance of obstructing secretions and hence in improvements in ventilation. We also hypothesised that exercise capacity would correlate with severity of lung disease as measured by ventilation heterogeneity on MRI.

The aims of this study were therefore to;

- i) Assess the effects of maximal exercise on ventilation MRI and MBW.
- ii) Assess the relationship of CPET metrics with ventilation MRI and MBW metrics.

1.2 Methods

1.2.1 Study design

This study forms part of a larger longitudinal study of LCI and MRI in children and adults with CF(16). In this interventional sub-study, patients performed MBW and imaging before and after a maximal CPET at one of their follow-up visits. Children and adults with CF were recruited from three specialist CF centres in the UK into the larger longitudinal study. Patients were eligible for this exercise sub-study if they were aged >10 years and if FEV₁ >30% and were not pre-selected. Patients were screened against the recommended CPET contraindications(20) and in addition patients with *Mycobacterium abscessus* or *Burkholderia cepacia* were excluded from the larger study, as were patients with a pulmonary exacerbation within the previous four weeks. In total 13 patients met the criteria and were assessed in this sub-study. The main limitation on participating in this sub-study were time constraints and the resulting potential patient fatigue after completing the rest of the protocol required for the longitudinal study. This study was approved by the Yorkshire and Humber - Leeds West Research Ethics Committee (REC reference: 16/YH/0339). All adult patients or parents of children provided written consent, children also provided written assent. Assessments took place between January 2017 and March 2019.

1.2.2 Assessment protocol

¹²⁹Xe or ³He MRI were performed on a 1.5T GE HDX MRI scanner (GE, Milwaukee, USA). Images were acquired at a lung volume of end-inspiratory tidal volume as previously described, using titrated inhaled volumes of test gas(16). A ¹H anatomical MRI was performed immediately prior to and at the same lung volume as the ¹²⁹Xe image. ¹H MRI was always re-acquired each time a ¹²⁹Xe image was performed and was used to calculate the thoracic cavity volume at which images were acquired. ¹²⁹Xe or ³He and ¹H MRI were segmented using a semi-automated Fuzzy C-means clustering method, as previously described (21), in order to calculate VDP and the ventilation heterogeneity index (VH_i)(16). More details on MRI sequences and gas doses can be found in the online supplement.

MBW was performed on an open-circuit Innocor (Pulmotrace, Glamsberg, Denmark) using 0.2% SF₆ as previously described(16, 22). Spirometry and body plethysmography were performed according to international recommendations(23, 24) on a 'PFT Pro'

(Vyaire, Basingstoke, UK). CPET was performed as recommended using a cycle ergometer and an 'Ultima' metabolic cart (Medical Graphics, Gloucester, UK)(6).

The first two patients to perform the exercise assessment were assessed with ^3He for ventilation MRI, and the remaining patients were assessed with ^{129}Xe , for reasons of gas availability and a switch to ^{129}Xe at our research centre. All patients performed the assessments in the same order. Ventilation MRI was performed first as a baseline measurement. This was followed by MBW and body plethysmography. A maximal CPET was then performed, followed by a repeat ventilation MRI within 30 minutes of the end of exercise. The repeat MBW was completed after this and spirometry was then performed at the end of the study visit. This sequence was the same for the two patients who were imaged with ^3He .

1.2.3 Analysis

The primary metrics used for analysis were VDP from MRI, LCI from MBW, VO_2peak from CPET, the residual volume to total lung capacity ratio (RV/TLC) from body plethysmography and FEV_1 from spirometry. Secondary outcomes include: VH_1 from ^{129}Xe MRI, VO_2AT (anaerobic threshold), Ve/VO_2 and Ve/VCO_2 at peak exercise from CPET and S_{cond} (convection-dependent ventilation heterogeneity) and S_{acin} (convection-diffusion dependent ventilation heterogeneity) from MBW. Prior to analysis, data were assessed for normal distribution using the Shapiro-Wilks test. An absolute change in VDP of $>\pm 1.6\%$ was used as the threshold above which a significant post-exercise response was determined, which represents the same-day repeatability of ^{129}Xe VDP in CF patients(25). The two subjects who were assessed with ^3He were removed from this analysis. Wilcoxon signed rank test was performed to compare the initial baseline values with the post-exercise values from MRI and MBW. ^3He and ^{129}Xe VDP values were pooled for quantitative analysis; previously we have shown that there is good agreement and minimal bias between the two gases in CF(26). Spearman's correlation was performed to compare exercise outcomes to ventilation MRI and lung function. A p-value of 0.05 was deemed statistically significant.

1.3 Results

Thirteen patients (including five patients under the age of 18 years), of whom five were female, completed the exercise study protocol. Patient demographics, and baseline lung function, MRI and CPET metrics are detailed in Table 1. Patients were aged between

10.2 and 43.7 years (mean age = 25.2 years) and had a spread of FEV₁ z-score values ranging from -4.4 to 0.92 (mean FEV₁ z-score = -1.8). Six patients had an FEV₁ within the normal range and five had a normal LCI (all of whom also had normal FEV₁). All patients achieved a maximal effort on CPET, as defined by achieving a respiratory exchange ratio (RER) >1.05(6).

Table 1: Baseline lung function, CPET and MRI metrics for the study population. Metrics are displayed for each individual patient within the study. Also documented are clinical demographics relating to the underlying CF and any previous diagnosis of asthma. Patient ^ indicates patients under the age of 18 years. FEV₁ – forced expiratory volume in one second. RV/TLC – the ratio of residual volume to total lung capacity. LCI – lung clearance index. S_{cond} – convection-dependent ventilation heterogeneity. S_{acin} – convection-diffusion-dependent ventilation heterogeneity. VDP – ventilation defect percentage. VH_i – ventilation heterogeneity index. VO₂peak – oxygen uptake at peak exercise. VO₂AT – oxygen uptake at the anaerobic threshold. Ve/VO₂ – the ratio of minute ventilation to oxygen uptake or the ventilatory equivalent for oxygen. Ve/VCO₂ – the ratio of minute ventilation to carbon dioxide production or the ventilatory equivalent for CO₂. Clinical data relates to the date of testing and was recorded from the patient notes. Pseudomonas refers to whether the patient was recorded as being chronically infected at the time of testing.

Patient	FEV ₁ z-score	RV/TLC %	LCI	S _{cond}	S _{acin}	VDP %	VH _i %	VO ₂ peak ml/min/kg	VO ₂ AT ml/min/kg	Ve/VO ₂	Ve/VCO ₂	Genotype	Pseudomonas Y/N	Asthma Y/N	Bronchodilator usage Y/N	CFTR modulator Y/N
1	-4.2	48.7	14.0	0.07	0.37	45.2	19.1	29.4	12.6	43.8	36.0	DF508/DF508	Y	N	Y	N
2	-0.5	29.0	7.4	0.09	0.08	1.5	10.0	30.7	12.2	59.1	42.0	DF508/DF508	N	N	N	N
3	-3.3	41.4	11.4	0.12	0.26	20.8*	19.0*	40.5	15.7	35.5	30.0	DF508/DF508	N	N	Y	N
4^	0.7	26.5	6.6	0.03	0.10	2.1*	9.4*	40.7	19.6	36.0	37.0	DF508/DF508	N	N	N	N
5	-2.7	34.4	9.4	0.14	0.22	17.8	12.3	38.1	18.9	39.0	31.0	R334W/R75X	N	N	N	N
6^	-0.9	24.0	7.3	0.11	0.06	2.0	9.0	31.6	15.1	52.9	48.0	DF508/DF508	N	Y	Y	N
7^	0.9	17.8	7.3	0.06	0.08	3.7	9.6	57.9	22.6	37.8	37.0	DF508/DF508	N	N	N	N
8	-2.4	31.0	8.2	0.07	0.23	7.3	15.4	37.4	18.7	46.0	33.0	DF508/DF508	Y	N	Y	N
9^	-0.5	22.0	7.6	0.11	0.09	2.7	9.5	49.1	19.1	48.9	37.0	DF508/Q493x	N	N	Y	N
10	-2.8	51.9	14.6	0.12	0.16	20.2	18.7	37.8	15.4	30.1	26.0	DF508/R553X	Y	N	N	N
11	-4.4	57.6	17.4	0.10	0.34	45.6	18.7	27.5	14.1	40.0	35.0	DF508/DF508	Y	N	Y	Orkambi
12^	-1.0	26.6	6.6	0.08	0.11	2.5	10.8	40.1	19.6	43.9	37.0	G551D/DF508	Y	N	Y	Ivacaftor
13	-2.8	45.3	13.0	0.15	0.14	30.8	19.5	33.8	14.3	42.5	34.0	DF508/W1282x	Y	N	Y	N

1.3.1 ¹²⁹Xe ventilation MRI: Baseline

At baseline, ventilation MRI defects were present in all patients. There was a wide range of disease severity with VDP ranging from 1.5 to 45.7%.

1.3.2 Ventilation MRI and MBW: Baseline and Post-CPET comparison

All patients successfully performed MRI and MBW post-CPET. There was a small but significant reduction in both VDP (p=0.04) and LCI (p=0.05) post-CPET when compared to baseline, but no significant change in VH_I , S_{cond} or S_{acin} (Table 2). The median difference (95% confidence intervals) for VDP showed a reduction of 1.5% (-0.4 to 3.0%) and for LCI a reduction of 0.4 units (-0.2 to 1.1) was observed. When the two patients who performed ³He were removed from the VDP analysis, the p-value changed to 0.15 and the median difference to 0.9% (-1.4 to 3.7%).

Table 2: Pre versus post CPET metrics for MRI and MBW for the whole group of patients. Data are displayed as either mean (SD) or median [IQR]. Statistically significant (p<0.05) changes in LCI and VDP post exercise as indicated by *.

	Baseline	Post-CPET
LCI	8.2 [7.3, 13.5]	7.8 [7.0, 12.0]*
S_{cond}	0.10 (0.03)	0.09 (0.04)
S_{acin}	0.17 (0.1)	0.18 (0.11)
VDP (%)	7.3 [2.3, 25.8]	7.1 [2.4, 24.8]*
VH_I (%)	12.3 [9.6, 19.0]	11.4 [9.8, 16.8]

Of the patients who performed the pre versus post exercise assessment with ¹²⁹Xe MRI, 5/11 patients had a change in VDP of $\geq \pm 1.6\%$. Of these five, four had a significant improvement in ventilation distribution and one had a significant worsening in the ventilation distribution (see Figure 1 for examples).

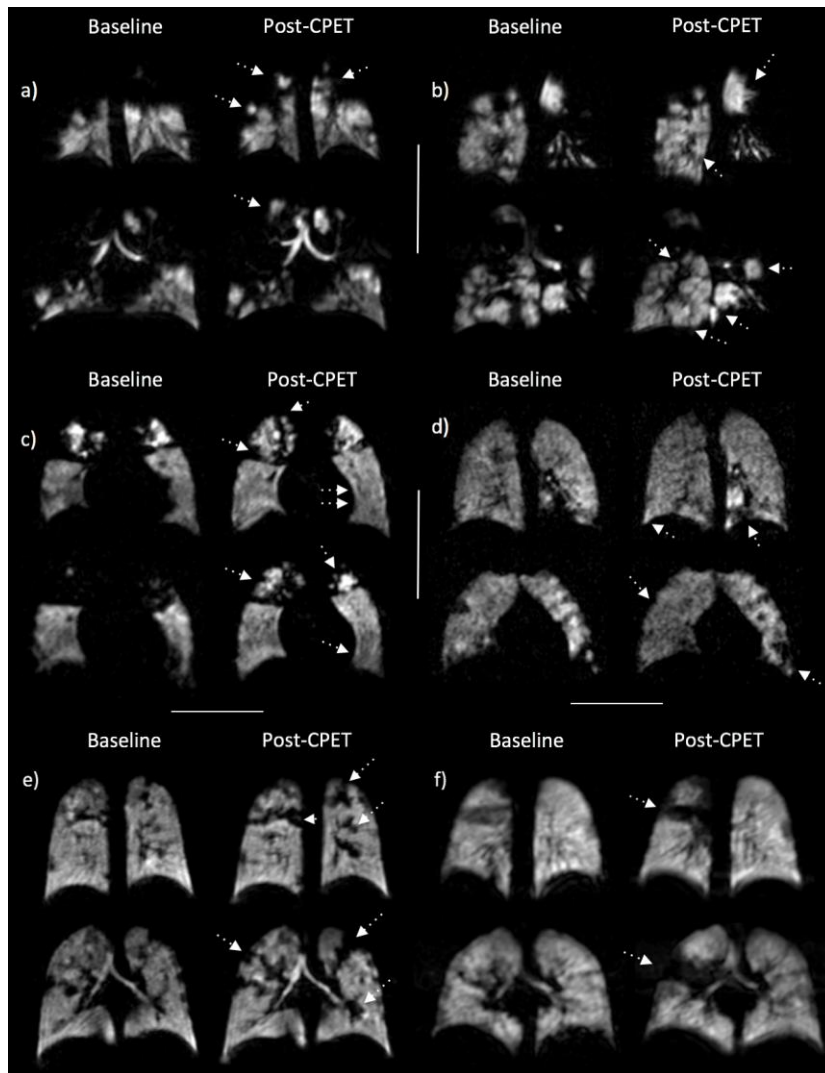


Figure 1: Representative ^{129}Xe ventilation image slices from six patients (a-f) at baseline and post-CPET. Two slice locations are shown per patient for comparison, depicting the change in ventilation that has occurred post-CPET. White dashed arrows in the post-CPET images highlight some of the areas of change in ventilation. Patients' a-d had an overall improvement in ventilation post-CPET, whilst patients' e and f had a worsening in ventilation post-CPET.

Patient a) had a reduction in absolute VDP of -3.7% (baseline to post-CPET VDP = 45.7 to 41.9%). Patient b) had a reduction in absolute VDP of -3.0% (baseline to post-CPET VDP = 45.2 to 42.2%). Patient c) had a reduction in absolute VDP of -5.9% (baseline to post-CPET VDP = 17.8 to 11.9%). Patient d) had a reduction in absolute VDP of -1.9% (baseline to post-CPET VDP = 3.7 to 1.8%). Patient e) had an increase in absolute VDP of 1.4% (baseline to post-CPET VDP = 2.0 to 3.4%). Patient f) had an increase in absolute VDP of 1.6% (baseline to post-CPET VDP = 1.5 to 3.1%). For both patients' e and f, the major areas of worsening ventilation post-CPET, appear to be in areas where ventilation defects were already present at baseline.

Of the remaining six patients assessed with ^{129}Xe MRI with a change in VDP of $<\pm 1.6\%$, only two had no clear visual change in the distribution of ventilation. The remaining patients with total VDP change $<\pm 1.6\%$ all had visible changes in ventilation. One of these had a visual worsening in overall ventilation (patient e, Figure 1) and the remaining three had an approximately equal combination of areas of improved and

decreased ventilation, with net change in VDP being small. The value of regional quantitative analysis is highlighted in Figure 1 (patient f), where the global change in VDP for this patient was 1.6%, however the change in the size of the defect evident in the right lung was 2.4%. The two patients assessed with ^3He also had a visible improvement in areas of ventilation abnormalities and had overall reductions in absolute VDP of -2.3% and -1.6%.

1.3.3 CPET metric comparisons with ventilation MRI and lung function

VO_2peak demonstrated significant correlations with RV/TLC ($r=-0.64$, $p=0.02$) and FEV_1 ($r=0.57$, $p=0.047$), whilst VO_2AT demonstrated correlations with RV/TLC ($r=-0.64$, $p=0.02$) and LCI ($r=-0.63$, $p=0.02$). Peak exercise Ve/VO_2 did not correlate with any imaging or lung function metrics. In contrast, peak exercise Ve/VCO_2 demonstrated significant correlations with VDP ($r=-0.72$, $p=0.007$), RV/TLC ($r=-0.70$, $p=0.01$), LCI ($r=-0.69$, $p=0.01$) and FEV_1 ($r=0.68$, $p=0.01$). VDP did not demonstrate a significant correlation with VO_2peak or VO_2AT (Figure 2).

Figure 2 shows the relationships between VDP and lung function metrics with VO_2peak and VO_2AT and the correlation metrics are detailed on each plot for all patients. The two patients who had a worsening of the distribution of ventilation post exercise (patients' e and f in Figure 1) appear to be outliers in that they had low values for VO_2 alongside well-preserved VDP and lung function. These two patients had similar levels of aerobic fitness to those with more severe lung disease, suggesting that these two patients were deconditioned. It is interesting that when these two patients data are removed from correlation analysis, the correlations of VO_2peak and VO_2AT with VDP become highly significant ($r=-0.78$, $p=0.006$ and $r=-0.92$, $p<0.001$ respectively). This observation was consistent for LCI ($r=-0.76$, $p=0.01$ and $r=-0.92$, $p<0.001$ respectively), FEV_1 ($r=0.81$, $p=0.004$ and $r=0.93$, $p<0.001$ respectively) and RV/TLC ($r=-0.86$, $p=0.001$ and $r=-0.92$, $p<0.001$ respectively).

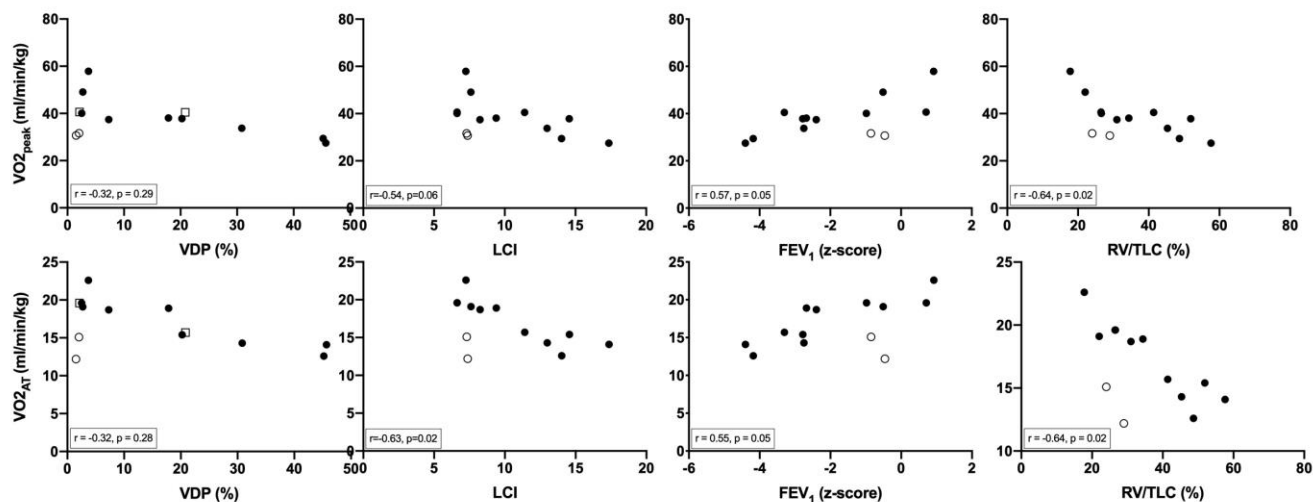


Figure 2: Scatter plots showing the relationships of VO₂peak and VO₂AT with pre-exercise VDP, LCI, FEV₁ and RV/TLC. Spearman correlation values are displayed representing analysis on all patients. The two patients highlighted by open-circles are the patients with a significant worsening in the distribution of ventilation post-CPET. These two patients appear to be outliers that have low fitness levels for their given degree of lung disease. The two patients highlighted in the plots of VDP with open-squares are the two patients where VDP was calculated from ³He MRI.

1.4 Discussion

In this cohort of patients with a broad range of age and lung disease, we have shown that by performing a maximal effort CPET, significant quantitative and visual changes in the distribution of ventilation were observed post-exercise in most patients. These data demonstrate the impact of exercise on lung ventilation.

There is increasing interest in and awareness of the effects of exercise on patients with CF(9, 10, 27, 28). Patients with reduced aerobic capacity have a greater risk of morbidity and mortality(2-4) and a greater risk of hospitalisation(5). When performing exercise, the physiological response is to increase minute ventilation. This increase in ventilation on exercise will result in the opening of some airways that were partially obstructed during quiet tidal breathing, a phenomenon we have previously demonstrated by comparing end tidal inspiration with maximal inspiration on ventilation MRI(16). This improvement in ventilation during exercise may allow for improved mucus clearance from the airways(7). The data presented here suggests that even by performing a short bout of maximal exercise in the form of a CPET, there are significant changes in the distribution of ventilation due to the movement of mucus.

These data add to the growing evidence base that exercise can be effective as a method of airway clearance. In a previous study, healthy trained subjects showed no change in ventilation heterogeneity measured using multi-breath washout following CPET(29). For most patients in the current study however (85%), the CPET caused a visible change in ventilation. Given the high intra-session repeatability of ^{129}Xe VDP(25), this suggests that the changes we observed in VDP and in the distribution of ventilation, relate to the underlying CF pathophysiology, and in part are likely a consequence of mucus movement in the airways. Change in VDP was greater than the intra-session repeatability of VDP, and therefore significant, for 45% of the patients assessed with ^{129}Xe . For four of these patients and for a further three without a significant change in VDP, there was an overall visible improvement in ventilation as was also the case for the two patients assessed with ^3He .

This illustrates a major advantage of ventilation MRI, namely that it provides detailed information as to the location and size of the regions of the lung that have changed. Global metrics of lung function, not only FEV₁ and LCI but also VDP, measure a minimal summary change when there are areas of the lung that change both positively and negatively by similar amounts, since the net effect can be close to zero. We have demonstrated here that patients without a significant change in VDP or lung physiology may still have large positive or negative changes in individual ventilation defects (for example patient f, Figure 1). Ventilation MRI can quantify ventilation defects in 3D providing regional lung function metrics, which more accurately reflects the regional effects of interventions(16).

The observation here that there were visible changes in ventilation for some patients without a change in VDP, is in keeping with previous studies where chest physiotherapy was performed pre and post ^3He ventilation MRI in children with CF(17-19). These studies showed that physiotherapy had an effect on the distribution of ventilation, but that whole lung VDP was similar post physiotherapy to baseline. In our study, a significant change in VDP was observed for some patients, which suggests that maximal exercise is performing effectively as a method of chest physiotherapy.

In this study, we observed a mean decrease in LCI post-exercise of 0.4. This is similar to the reduction in LCI reported previously post-CPET, where the authors reported a reduction in LCI of 0.7(9). It is recommended that all patients with CF perform some form of airway clearance as part of their routine management(1), but the evidence for

one single method over another is limited(30). One reason for this may be that the outcome measure utilised is usually the change in FEV₁(30). It is now well recognised that FEV₁ lacks sensitivity to detect small meaningful changes in the lungs and may be a reason why exercise trials in CF have not shown statistically significant improvements in lung function(10). More sensitive summary measurements of lung function such as LCI may be more suitable in those with mild-moderate disease, but only MRI provides the detailed regional information across the full spectrum of disease.

Patients' e and f in Figure 1 were the only two patients assessed where there was a visible worsening of ventilation post exercise. Patient e had a previous diagnosis of asthma, raising the possibility that the worsening in ventilation could be caused by exercise induced bronchospasm. There was no corresponding change in this patients FEV₁, which was within the normal range without evidence of significant airflow obstruction, so any bronchospasm that occurred was undetectable by conventional means. In these two cases, re-distribution of mucus into larger airways is also a plausible explanation. Movement of mucus into more proximal airways would cause larger ventilation defects to appear distal to the mucus. In this scenario, despite a temporary worsening in overall ventilation, the clinical effect may ultimately be positive due to the proximal movement of mucus, which is expectorated at a later time point. These two patients however also showed discrepancy between their baseline lung function and CPET markers, with low aerobic capacity and relatively well preserved lung function. As such, they would be considered deconditioned and regular exercise would be recommended to help this. An intriguing possibility also exists: that the short term worsening of ventilation heterogeneity is a regular feature of their response to exercise, and could be a factor in their deconditioning. Excluding these two outliers from correlation analysis, the relationship of VDP with VO₂ metrics is significant, supporting that in most cases there is a relationship between underlying lung disease and aerobic capacity. When all patients were assessed we also found that Ve/VCO₂ at peak exercise was highly correlated to VDP. This is an intuitive relationship as Ve/VCO₂ is a metric of ventilation efficiency and higher values for VDP would infer ventilation inefficiency due to increased physiological dead-space within the lungs.

The main limitation to this study is the small number of patients involved. However, this was an intensive study, with a detailed analysis. Two patients were assessed using ³He, but recent work has demonstrated high concordance and minimal bias between ³He and ¹²⁹Xe(26, 31) ventilation MRI, and this is unlikely to have affected the main conclusion

that exercise often changes the distribution of ventilation in patients with CF. We also were unable to assess any change in FEV₁ with exercise, with only post-exercise spirometry performed. Spirometry however was not the primary method for comparison and a pre-exercise spirometry would have potentially affected the distribution of ventilation as measured on ¹²⁹Xe MRI and LCI. We were also only able to assess the short-term impact of a maximal exercise session performed under clinical supervision, and home exercise regimens may not match the intensity. Longer-term effects may also differ for exercise and formal chest physiotherapy. These limitations could be explored further in longer-term exercise trials, as could the effect of exercise on lung perfusion, which we were unable to measure in this study.

1.5 Conclusion

In conclusion, we have shown that maximal exercise has an acute effect on the distribution of ventilation in CF, and that increasing VDP is likely associated with decreasing exercise capacity. This work demonstrates that maximal exercise has an effect on airway clearance and supports recommendations that exercise is beneficial. Ventilation MRI is an ideal methodology for assessing the re-distribution of ventilation caused by exercise and physiotherapy interventions.

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1.8 References

1. Smyth AR, Bell SC, Bojcin S, Bryon M, Duff A, Flume P, et al. European Cystic Fibrosis Society Standards of Care: Best Practice guidelines. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society*. 2014;13 Suppl 1:S23-42.
2. Nixon PA, Orenstein DM, Kelsey SF, Doershuk CF. The prognostic value of exercise testing in patients with cystic fibrosis. *The New England journal of medicine*. 1992;327(25):1785-8.
3. Pianosi P, Leblanc J, Almudevar A. Peak oxygen uptake and mortality in children with cystic fibrosis. *Thorax*. 2005;60(1):50-4.
4. Hebestreit H, Hulzebos EHJ, Schneiderman JE, Karila C, Boas SR, Kriemler S, et al. Cardiopulmonary Exercise Testing Provides Additional Prognostic Information in Cystic Fibrosis. *Am J Respir Crit Care Med*. 2019;199(8):987-95.
5. Perez M, Groeneveld IF, Santana-Sosa E, Fiuza-Luces C, Gonzalez-Saiz L, Villa-Asensi JR, et al. Aerobic fitness is associated with lower risk of hospitalization in children with cystic fibrosis. *Pediatric pulmonology*. 2014;49(7):641-9.
6. Hebestreit H, Arets HG, Aurora P, Boas S, Cerny F, Hulzebos EH, et al. Statement on Exercise Testing in Cystic Fibrosis. *Respiration*. 2015;90(4):332-51.
7. Dwyer TJ, Daviskas E, Zainuldin R, Verschuer J, Eberl S, Bye PTP, et al. Effects of exercise and airway clearance (PEP) on mucus clearance in cystic fibrosis: a randomised cross-over trial. *European Respiratory Journal*. 2019:1801793.
8. Rowbotham NJ, Smith S, Leighton PA, Rayner OC, Gathercole K, Elliott ZC, et al. The top 10 research priorities in cystic fibrosis developed by a partnership between people with CF and healthcare providers. *Thorax*. 2018;73(4):388-90.
9. Tucker MA, Crandall R, Seigler N, Rodriguez-Miguel P, McKie KT, Forseen C, et al. A single bout of maximal exercise improves lung function in patients with cystic fibrosis. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society*. 2017;16(6):752-8.
10. Ward N, Stiller K, Rowe H, Morrow S, Morton J, Greville H, et al. Airway clearance by exercising in mild cystic fibrosis (ACE-CF): A feasibility study. *Respir Med*. 2018;142:23-8.
11. Main E, Grillo L, Rand S. Airway clearance strategies in cystic fibrosis and non-cystic fibrosis bronchiectasis. *Semin Respir Crit Care Med*. 2015;36(2):251-66.
12. 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(8):760-2.
13. Smith L, Marshall H, Aldag I, Horn F, Collier G, Hughes D, et al. Longitudinal Assessment of Children with Mild Cystic Fibrosis Using Hyperpolarized Gas Lung Magnetic Resonance Imaging and Lung Clearance Index. *American journal of respiratory and critical care medicine*. 2018;197(3):397-400.

14. Altes TA, Johnson M, Fidler M, Botfield M, Tustison NJ, Leiva-Salinas C, et al. Use of hyperpolarized helium-3 MRI to assess response to ivacaftor treatment in patients with cystic fibrosis. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society*. 2017;16(2):267-74.
15. 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. *The European respiratory journal*. 2019;53(5):1802188.
16. Smith LJ, Collier GJ, Marshall H, Hughes PJC, Biancardi AM, Wildman M, et al. Patterns of regional lung physiology in cystic fibrosis using ventilation magnetic resonance imaging and multiple-breath washout. *The European respiratory journal*. 2018;52(5).
17. Woodhouse N, Wild JM, van Beek EJ, Hoggard N, Barker N, Taylor CJ. Assessment of hyperpolarized 3He lung MRI for regional evaluation of interventional therapy: a pilot study in pediatric cystic fibrosis. *J Magn Reson Imaging*. 2009;30(5):981-8.
18. Bannier E, Cieslar K, Mosbah K, Aubert F, Duboeuf F, Salhi Z, et al. Hyperpolarized 3He MR for sensitive imaging of ventilation function and treatment efficiency in young cystic fibrosis patients with normal lung function. *Radiology*. 2010;255(1):225-32.
19. Mentore K, Froh DK, de Lange EE, Brookeman JR, Paget-Brown AO, Altes TA. Hyperpolarized HHe 3 MRI of the lung in cystic fibrosis: assessment at baseline and after bronchodilator and airway clearance treatment. *Acad Radiol*. 2005;12(11):1423-9.
20. ATS. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. 2003;167(2):211-77.
21. Hughes PJC, Horn FC, Collier GJ, Biancardi A, Marshall H, Wild JM. Spatial fuzzy c-means thresholding for semiautomated calculation of percentage lung ventilated volume from hyperpolarized gas and (1) H MRI. *J Magn Reson Imaging*. 2018;47(3):640-6.
22. Horsley AR, Gustafsson PM, Macleod KA, Saunders C, Greening AP, Porteous DJ, et al. Lung clearance index is a sensitive, repeatable and practical measure of airways disease in adults with cystic fibrosis. *Thorax*. 2008;63(2):135-40.
23. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *American journal of respiratory and critical care medicine*. 2019;200(8):e70-e88.
24. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. *The European respiratory journal*. 2005;26(3):511-22.
25. Smith LJ, Horsley A, Bray J, Hughes PJC, Biancardi A, Norquay G, et al. The assessment of short and long term changes in lung function in CF using 129Xe MRI. *European Respiratory Journal*. 2020:2000441.
26. Smith L, Collier G, Marshall H, Hughes P, Biancardi A, Norquay G, et al. Clinical applicability of 3He and 129Xe ventilation MRI in cystic fibrosis: longitudinal follow up. *European Respiratory Journal*. 2019;54(suppl 63):PA334.
27. Vendrusculo FM, Johnstone Z, Dhouieb E, Donadio MVF, Cunningham S, Urquhart DS. Airway clearance physiotherapy improves ventilatory dynamics during exercise in patients with cystic fibrosis: a pilot study. *Archives of disease in childhood*. 2018.
28. Radtke T, Boni L, Bohnacker P, Maggi-Beba M, Fischer P, Kriemler S, et al. Acute effects of combined exercise and oscillatory positive expiratory pressure therapy on sputum properties and lung diffusing capacity in cystic fibrosis: a randomized, controlled, crossover trial. *BMC Pulm Med*. 2018;18(1):99.
29. Wrobel JP, Ellis MJ, Kee K, Stuart - Andrews CR, Thompson BR. Maximal exercise does not increase ventilation heterogeneity in healthy trained adults. *Physiological reports*. 2016;4(7).
30. Main E. Airway clearance research in CF: the 'perfect storm' of strong preference and effortful participation in long-term, non-blinded studies. *Thorax*. 2013;68(8):701-2.

31. Woods JC, Wild JM, Wielputz MO, Clancy JP, Hatabu H, Kauczor HU, et al. Current state of the art MRI for the longitudinal assessment of cystic fibrosis. *J Magn Reson Imaging*. 2019;n/a(n/a).