THE IMPLICATIONS OF DYSGLYCAEMIA ON AEROBIC EXERCISE AND VENTILATORY FUNCTION IN CYSTIC FIBROSIS

Running title: Glycaemia, exercise and ventilatory function in CF

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ABSTRACT

Background: The development of cystic fibrosis (CF)-related diabetes (CFRD) in paediatric groups is associated with a reduced aerobic fitness. However, this has yet to be investigated in adults with more severe lung disease.

Methods: Cardiopulmonary exercise and glycaemic control tests were retrospectively analysed in 46 adults with CF (age: 26.9 y [range: 16.3–66.5 y]; forced expiratory volume in 1s: 65.3% [range: 26.8–105.7%]; 26 males), diagnosed with CFRD (n = 19), impaired glucose tolerance (IGT; n = 8) or normal glucose tolerance (NGT; n = 19).

Results: Maximal oxygen uptake ($\dot{V}O_{2max}$) was reduced in adults with IGT and CFRD compared to their age- and gender-matched counterparts with NGT ($p < 0.05$); however, there was no difference when lung function was included as a covariate (all $p > 0.05$). $\dot{V}O_{2max}$ was greater in adults who experienced post-reactive hypoglycaemia vs. NGT without hypoglycaemia ($p < 0.05$). The frequency of ventilatory limitation (84%, 63% and 37%, respectively; $p < 0.05$) but not ventilation-perfusion mismatch (42%, 38% and 16%, respectively; $p > 0.05$), was greater with CFRD and IGT vs. NGT. There was also no difference in arterial oxygen saturation changes between groups ($p > 0.05$). Gender and body mass index were significant predictors of $\dot{V}O_{2max}$ (adjusted $R^2 = 0.37$, $p < 0.01$), but glycaemic control did not explain additional variance ($p > 0.05$).

Conclusions: Adults with CF-related dysglycaemia had a reduced $\dot{V}O_{2max}$ compared to age- and gender-matched counterparts, due to a greater degree of CF lung disease in these populations.

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HIGHLIGHTS

1. $\dot{V}O_{2max}$ was significantly reduced in adults with CF-related dysglycaemia, except when FEV_1 and FVC were included as covariates;
2. $\dot{V}O_{2max}$ was increased in adults with CF who experience post-reactive hypoglycaemia;
3. CF-related dysglycaemia was associated with abnormal ventilation during exercise;
4. Gender and nutritional status were modulators of $\dot{V}O_{2max}$ in CF.

Keywords: Cardiorespiratory fitness; cystic fibrosis-related diabetes; maximal oxygen uptake; respiratory disease.

ABBREVIATIONS

SpO_2	Arterial oxygen saturation
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
B	Regression slope coefficient
BMI	Body mass index
CF	Cystic fibrosis
CFRD	Cystic fibrosis-related diabetes
CFTR	Cystic fibrosis transmembrane conductance regulator
CPET	Cardiopulmonary exercise testing
FEV_1	Forced expiratory volume in 1 second
FPG	Fasting plasma glucose
FVC	Forced vital capacity
GET	Gas exchange threshold
HbA1c	Glycated haemoglobin
HR	Heart rate
IGT	Impaired glucose tolerance
IVAB	Intravenous antibiotics
MVV	Maximal voluntary ventilation
n	Sample size
n^2	Partial-eta squared
NGT	Normal glucose tolerance
OGTT	Oral glucose tolerance

88	*P. aeruginosa*	Pseudomonas aeruginosa
89	PRH	Post-reactive hypoglycaemia
90	*r*	Pearson's correlation coefficient
91	RPE	Ratings of perceived exertion
92	SD	Standard deviation
93	SE	Standard error
94	S_{max}	Supramaximal verification
95	SpO_2	Arterial oxygen saturation
96	$\Delta\dot{V}_E/\Delta\dot{V}CO_2$	Ventilatory drive
97	$\dot{V}CO_2$	Carbon dioxide production
98	$\dot{V}_E$	Minute ventilation
99	$\dot{V}_{Epeak}$	Peak minute ventilation
100	$\dot{V}_E$/MVV	Breathing reserve
101	$\dot{V}_E/\dot{V}O_2$	Ventilatory equivalent of oxygen
102	$\dot{V}_E/\dot{V}O_{2peak}$	Peak ventilatory equivalent of oxygen
103	$\dot{V}_E/\dot{V}CO_2$	Ventilatory equivalent of carbon dioxide
104	$\dot{V}_E/\dot{V}CO_{2peak}$	Peak ventilatory equivalent of carbon dioxide
105	$\dot{V}O_2$	Oxygen uptake
106	$\dot{V}O_{2max}$	Maximal oxygen uptake
107	$\dot{V}O_{2peak}$	Peak oxygen uptake
108		
109		

BACKGROUND

The primary cause of mortality in cystic fibrosis (CF) is respiratory failure, however, the increasing survival age means that non-respiratory consequences have a greater bearing upon quality and longevity of life [1]. For example, approximately 35% of adults with CF develop CF-related diabetes (CFRD) [1]. CFRD is associated with a greater decline in lung function [2], worsened nutritional status [3] and poorer prognosis [4]. Cardiopulmonary exercise testing (CPET) is advocated by both the European CF Society and European Respiratory Society [5,6] as a routine clinical assessment. This is because higher levels of aerobic fitness (peak oxygen uptake [$\dot{V}O_{2peak}$]) are associated with an improved quality of life [7], reduced risk of being hospitalised with a pulmonary exacerbation [8] and better prognosis [9]. To date, ventilatory [10], cardiac [11], vascular [12,13] and skeletal muscle [14] abnormalities have been reported to modulate aerobic fitness in CF. However, only a small number of studies have investigated the impact of CF-related dysglycaemia on outcomes from CPET [15,16].

Lower $\dot{V}O_{2peak}$ [15] and peak power output [16] have been reported in children and adolescents with CFRD compared to those with CF and normal or impaired glucose tolerance (NGT and IGT, respectively). However, no difference in 6 min walk test performance was reported between adults with NGT, IGT and CFRD, although a greater exercise-induced reduction in arterial O_2 saturation (SpO_2) was observed in those with IGT [17]. This latter finding may suggest an abnormal ventilatory response to exercise in people with CF-related dysglycaemia [5]. Importantly, ventilatory parameters have been shown to be associated with prognosis in CF [9] and are more sensitive to changes in CF lung disease than $\dot{V}O_{2peak}$ [10]. However, previous studies investigating the relationships between dysglycaemia and aerobic fitness were limited by sample size [16], focusing largely on children and adolescents with mild lung disease [15] and/or inaccuracies in the

exercise testing protocols used [17]. There is a need, therefore, to investigate the relationships between dysglycaemia, aerobic exercise and ventilatory function across the spectrum of CF severity.

This study was designed to investigate whether there are differences in aerobic exercise and ventilatory function between adults with CF and NGT, IGT or CFRD. It was hypothesised that *(1)* adults with IGT and CFRD would have a reduced $\dot{V}O_{2max}$ and earlier occurrence of the gas exchange threshold (GET) compared to age- and gender-matched adults with CF and NGT; *(2)* greater frequency of ventilatory limitation during CPET would cause a greater reduction in SpO_2 in adults with CFRD compared to age- and gender-matched adults with CF and NGT; and *(3)* the inclusion of glycaemic control variables within a multiple linear regression model would significantly improve the explained variance of $\dot{V}O_{2max}$ in adults with CF.

MATERIALS AND METHODS

Study design

This study was a retrospective analysis of data collected during out-patient clinic visits at the Adult Wessex CF Unit. Participants were included if they completed CPET and oral glucose tolerance testing (OGTT; or they had an existing diagnosis of CFRD) between July 2017 - August 2018. Participants with CFRD were age- and gender-matched to an individual with CF and NGT (± 2 years). All participants had a diagnosis of CF based on a clinical picture in keeping with CF, elevated sweat chloride levels (> 60 $mmol \cdot L^{-1}$) and a compatible genotype [18]. As the findings presented are a retrospective analysis of de-identifiable data, this study was exempted from National Health Service Research Ethics Committee approval.

155 *Glycaemic control*

156 All participants were screened for CFRD in line with the American Diabetes Association
157 guidelines [19]. Glucose lowering therapies were omitted on the morning of OGTT. Participants
158 who were fasted overnight (≥ 10 h) undertook a 2 h OGTT of 1.75 $g \cdot kg^{-1}$ (maximum of 75 g) of
159 anhydrous glucose during a morning clinic. CFRD was diagnosed if 2 h plasma [glucose] was ≥
160 11.1 $mmol \cdot L^{-1}$ and confirmed on a separate day by either a repeat OGTT, fasting plasma [glucose]
161 ≥ 7 $mmol \cdot L^{-1}$, glycated haemoglobin (HbA1c) ≥ 48 $mmol \cdot mol^{-1}$ or the presence of symptoms
162 linked with diabetes (polyuria and polydipsia). IGT was diagnosed if 2 h plasma [glucose] was
163 7.8-11.0 $mmol \cdot L^{-1}$ or fasting plasma [glucose] was ≥ 6.3 $mmol \cdot L^{-1}$. Post-reactive hypoglycaemia
164 (PRH) was defined by 2 h plasma [glucose] ≤ 3.9 $mmol \cdot L^{-1}$.

165 *CPET procedures*

166 Lung function was assessed using flow-volume spirometry (3500 MicroLab Spirometer MK8,
167 CareFusion, CA, USA), in accordance with the British Thoracic Society guidelines [20]. Forced
168 expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were determined as the highest
169 of three consistent (≤ 5% variability) manoeuvres and presented as a percentage of the Global
170 Lung Function Initiative (2012) reference values [21].

171 Our centre employs a combined ramp incremental and supramaximal verification (S_{max}) CPET
172 protocol on a cycle ergometer (Lode Corival, Groningen, The Netherlands; this protocol is
173 comprehensively described elsewhere: [22]). Breath-by-breath pulmonary gas exchange and
174 ventilation (K5, COSMED, Rome, Italy), beat-by-beat heart rate (HR; Premium HR Monitor,
175 Garmin, KS, USA) and fingertip SpO_2 were measured throughout exercise. Exercise was
176 terminated if SpO_2 dropped ≤ 85%. Subjective ratings of perceived exertion (RPE) were measured

177 using the Borg 6-20 scale [23]. Dyspnoea was measured using the 0-10 category-ratio scale [23]
178 every 1 min throughout exercise.

179 *CPET Analysis*

180 A 'maximal' effort during the ramp test was accepted when S_{max}-$\dot{V}O_{2peak}$ did not exceed ramp-
181 $\dot{V}O_{2peak}$ by ≥ 9% or a $\dot{V}O_2$ plateau was present upon exhaustion [22], with a plateau determined
182 using methodology comprehensively described elsewhere [24]. HR, $\dot{V}O_2$, carbon dioxide
183 production ($\dot{V}CO_2$), minute ventilation ($\dot{V}_E$) and ventilatory equivalents of O_2 ($\dot{V}_E/\dot{V}O_2$) and CO_2
184 ($\dot{V}_E/\dot{V}CO_2$) data were interpolated to 15 s averages and peak values taken as the highest 15 s average
185 achieved during the ramp incremental test.

186 $\dot{V}O_{2max}$ was taken as the highest 15 s average from either the ramp incremental or S_{max} tests. GET
187 was determined using the V-slope method [25] and confirmed through visual inspection of the
188 ventilatory equivalents. O_2 pulse, an index of stroke volume, was calculated by expressing $\dot{V}O_2$ as
189 a function of HR ($mL \cdot beat^{-1}$). Ventilatory drive ($\Delta\dot{V}_E/\Delta\dot{V}CO_2$) was determined by plotting a linear
190 regression line through the power output x $\dot{V}_E/\dot{V}CO_2$ response up to the respiratory compensation
191 point [26]. A ventilatory-perfusion mismatch was considered evident if $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ was ≥ 34 [26].
192 Breathing reserve ($\dot{V}_E$/MVV) was calculated by expressing $\dot{V}_{Epeak}$ as a percentage of predicted
193 maximal voluntary ventilation (MVV [27] = FEV_1 (in L) x 40).

194 *Statistical Analysis*

195 Data were expressed as means ± standard deviations unless otherwise stated. Statistical
196 significance was set at $\alpha = 0.05$. Analysis of variance (ANOVA) tests were conducted to determine
197 differences between the groups' anthropometric and clinical data (Table 1). A series of analysis of
198 covariance (ANCOVA) tests were subsequently used to determine between group differences in

aerobic exercise, ventilatory and cardiovascular function during CPET. Principle component analysis was used to compute a 2-component score of lung function, where 93.1% and 6.9% of the variance was explained by FEV_1 and FVC, respectively. The 2-component score was included as a single covariate in ANCOVA. Tukey's HSD or Games-Howell post-hoc *t*-tests were conducted on homogeneous and heterogeneous data, respectively. Chi-squared tests were used to determine significant difference in nominal variables. Measures of effect sizes were reported as partial eta-squared (η^2).

Pearson's correlation coefficients were used to determine associations between variables. Hierarchical multiple linear regression models were used to determine predictors of $\dot{V}O_{2max}$. A significant multiple regression model of gender, age, body mass index (BMI), FEV_1, FVC, pancreatic sufficiency and intravenous antibiotic days over 12 months (IVAB) was computed. The variables of dysglycaemia (i.e. IGT and CFRD, yes vs. no) and HbA1c were then entered to determine whether glycaemic control explains significantly more variance of $\dot{V}O_{2max}$. Statistical analyses were performed using SPSS v.24.0 (IBM, IL, USA).

RESULTS

Participant and CPET information

Forty-six adults were eligible for inclusion in this analysis as they achieved $\dot{V}O_{2max}$ and undertook an OGTT (or had previously been diagnosed with CFRD) in the given period, with the average time between CPET and OGTT being 4 ± 2 months. Characteristics of the included participants are presented in Table 1. Nineteen of the 46 participants were diagnosed with CFRD (time since diagnosis: 5.0 ± 5.3 y), of which 1 was prescribed with metformin alone (for the treatment of

polycystic ovary syndrome), and 10 received a combination of short- and long-acting insulin injections. The participants who did not receive glucose lowering therapies were either diet controlled (n = 5) or monitoring blood glucose levels (n = 3).

Aerobic fitness

$\dot{V}O_{2max}$ (% predicted only) was significantly reduced in adults with CFRD and IGT compared to age- and gender-matched controls with CF and NGT ($p < 0.05$). Notably, however, ANCOVA including FEV_1 and FVC as covariates revealed no significant differences in maximal ($\dot{V}O_{2max}$) or submaximal (GET) parameters of aerobic fitness between age- and gender-matched groups with NGT, IGT or CFRD (Figure 1). Subgroup analysis also revealed those who experienced PRH during OGTT (n = 8) had a significantly greater $\dot{V}O_{2max}$ vs. those with NGT without PRH (n = 11; Figure 2).

There were no significant differences in peak power output, expressed in absolute terms (181 ± 60 vs. 139 ± 47 vs. 156 ± 47 W, p = 0.87, n^2 = 0.01) or relative to body mass (2.8 ± 0.9 vs. 2.2 ± 0.6 vs. 2.5 ± 0.6 W·kg^{-1}, p = 0.82, n^2 = 0.01) between the NGT, IGT or CFRD groups, respectively.

Ventilatory and cardiovascular parameters

There was no significant difference in ΔSpO_2 between adults with NGT, IGT or CFRD (NGT: -3 ± 3 vs. IGT: -4 ± 2 vs. CFRD: -3 ± 3%; p = 0.62, n^2 = 0.03), but there was a significant difference in dyspnoea at exhaustion between adults with NGT vs. CFRD (NGT: 7 ± 2 vs. IGT: 7 ± 2 vs. CFRD: 6 ± 2, p = 0.03, n^2 = 0.17). Notably, absolute SpO_2 values of < 90% were experienced in 10.5% and 11.1% of adults with CFRD and IGT, respectively, but no adults with NGT.

There were no significant differences in the $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ (Figure 1), $\dot{V}_E$/MVV (Figure 1), $\dot{V}_{Epeak}$ (96.0 ± 31.1 vs. 80.0 ± 22.7 vs. 86.6 ± 23.5 L·min^{-1}, p = 0.89, n^2 = 0.01), $\dot{V}_E/\dot{V}CO_2$ at GET (Figure

1), $\dot{V}_{E}/\dot{V}CO_{2peak}$ (38.1 ± 5.3 vs. 43.7 ± 5.8 vs. 39.9 ± 6.5 L·min^{-1}, p = 0.18, n^2 = 0.08) or $\dot{V}_{E}/\dot{V}O_{2peak}$ (41.3 ± 6.1 vs. 41.7 ± 5.8 vs. 42.8 ± 7.7 L·min^{-1}, p = 0.42, n^2 = 0.04) between the NGT, IGT or CFRD groups, respectively. Notably, a significantly higher proportion of participants with CFRD and IGT presented with ventilatory limitation (NGT: 37% vs. IGT: 63% vs. CFRD: 84%; $p < 0.01$), but not ventilatory-perfusion mismatch (NGT: 16% vs. IGT: 38% vs. CFRD: 42%; p = 0.19) vs. the NGT group.

There were no significant differences in HR_{peak} (178 ± 13 vs. 171 ± 9 vs. 174 ± 10 beats·min^{-1}, p = 0.94, $n^2 < 0.01$) or peak O_2 pulse (14.3 ± 3.4 vs. 13.6 ± 4.7 vs. 12.9 ± 3.5 mL·beat^{-1}, p = 0.84, n^2 = 0.01) between the NGT, IGT or CFRD groups, respectively.

Predictors of aerobic fitness in those with- and without-CFRD

Overviews of the regression and correlation analyses are presented in Tables 2 and 3, respectively. The inclusion of age, gender, BMI, FEV_1, FVC, pancreatic sufficiency status and days on IVAB resulted in a significant regression model of $\dot{V}O_{2max}$ relative to body weight with an adjusted R^2 of 0.37 ($F_{(7,36)}$ = 4.67, $p < 0.01$). The inclusion of HbA1c and glycaemic control status did not significantly increase the explained variance (R^2 change = 0.03, p = 0.33).

DISCUSSION

This is the first study to investigate the impact of dysglycaemia upon the aerobic exercise and ventilatory function of adults with mild to severe CF lung disease. Three key findings were observed: *(1)* $\dot{V}O_{2max}$ as a percentage predicted was reduced in adults with CFRD and IGT compared to their counterparts with NGT, which was dependent on the groups with CFRD and IGT having a greater severity of lung disease *(2)* ΔSpO_2 did not significantly differ between age-

and gender-matched groups despite ventilatory limitation during maximal exercise being more prevalent in adults with CFRD compared to NGT; and *(3)* variance in $\dot{V}O_{2max}$ was primarily explained by gender and BMI in adults without CFRD, with glycaemic control explaining no additional variance.

The key finding of the present study was that $\dot{V}O_{2max}$, as a percentage predicted, was reduced in people with CFRD and IGT compared to their counterparts with NGT. Furthermore, 57% of adults with CFRD were at a heightened mortality risk (i.e. $\dot{V}O_{2max} \leq 81\%$ [9]), compared to only 21% of the NGT group. Interestingly, when FEV_1 and FVC were included as covariates the statistical significance in $\dot{V}O_{2max}$ between groups was not evident (Figure 1), suggesting that advanced lung disease in adults with CF-related dysglycaemia was the primary modulator of aerobic fitness in comparison to their counterparts with NGT. The latter finding is in contrast to previous reports, where $\dot{V}O_{2peak}$ was reduced in paediatric participants with CFRD compared to their NGT counterparts even after FEV_1 was included as a covariate [15]. Notably, this could be due to the adult NGT group in the present study having a worse $\dot{V}O_{2max}$ compared to the $\dot{V}O_{2peak}$ values reported for the children and adolescents with mild-to-moderate CF lung disease (38.9 ± 9.7 vs. 41.3 ± 9.4 $mL \cdot kg \cdot min^{-1}$, respectively) [15]. Furthermore, adults with CF-related dysglycaemia underwent significantly more IVAB days than their counterparts with NGT, which could indicate a greater interaction with physiotherapy staff who are likely to promote physical activity. Therefore, it would be of interest for future prospective trials to measure physical activity alongside CPET to account for such covariance.

The secondary finding of the present study was that ΔSpO_2 during CPET was not significantly different between groups, which is contrast to previous reports in adults who reported that ΔSpO_2 was significantly greater in those with CF-related dysglycaemia vs. NGT [17]. This was somewhat

surprising given that 84% of participants with CFRD were ventilatory limited during CPET compared to 37% of those with NGT (Figure 1). Despite a greater frequency of ventilatory limitation in those with CFRD, it is important to note that there were no significant differences between groups in $\dot{V}_E$/MVV, or other prognostically relevant outcomes such as $\dot{V}_E/\dot{V}O_{2peak}$ and $\dot{V}_E/\dot{V}CO_{2peak}$ (Figure 1). Interestingly, in the present study, the values reported for $\dot{V}_E$/MVV, $\dot{V}_E/\dot{V}O_{2peak}$ and $\dot{V}_E/\dot{V}CO_{2peak}$ in adults with CF, irrespective of glycaemic status, were comparable to the clusters at greatest risk of mortality [9]. This evidence supports contemporary suggestions in predominantly paediatric groups that the development of CFRD does not significantly reduce survival probability [9]. Conversely, a medium effect size ($n^2 = 0.11$) suggested that $\Delta\dot{V}_E/\Delta\dot{V}CO_2$ may be elevated in those with CF-related dysglycaemia, even after accounting for the influence of FEV_1 and FVC. These findings suggest that additional variables, that are not included in our study, may modulate aerobic exercise and ventilatory function in CF. For example, CFTR expression in the endothelium could cause microvascular dysfunction in the lung [28], a parameter which is exacerbated by the inflammation and oxidative stress which result from dysglycaemia [29].

In accordance with previous data in children and adolescents [15,16], the present study did not find a significant correlation between $\dot{V}O_{2max}$ and HbA1c in adults with CFRD (Table 3). Notably, the use of HbA1c has been debated in CF because it does not distinguish between variable bouts of hypo- and hyperglycaemia as opposed to time spent within an optimal range of blood glucose levels [30]. Additionally, glycaemic control variables did not explain a significant proportion of the variance in $\dot{V}O_{2max}$ between participants. Instead, variance in $\dot{V}O_{2max}$ was primarily explained by gender and BMI (Table 2). The only parameter of cardiac function in the present study, O_2 pulse, was not significantly different between groups. However, cardiovascular parameters in other

studies have been highlighted as modulators of aerobic fitness [11–13], and the inclusion of more investigative parameters may have improved the present study's multiple regression model.

Interestingly, the only group with a $\dot{V}O_{2max}$ of ≥ 100% predicted was those who experienced PRH during OGTT (Figure 2). PRH is a phenomenon of NGT in people with CF, reportedly present in 7-69% of people with CF without diabetes (18% in the present study; [31]). Traditionally, PRH was considered a precursor to the development of CFRD, where delayed, increased and extended insulin responses have been proposed as potential mechanisms [31,32]. More recently, however, large trials with 3.5 y [33] and 10 y [34] follow-up durations have shown no association between PRH and the development of CFRD and, instead, have demonstrated improved clinical outcomes [34,35]. Interestingly, reports have also observed a reduced insulin response at 2 h of an OGTT in those who experience PRH [35], therefore, implicating improved insulin sensitivity in the aetiology of PRH. Notably, similar mechanisms have been postulated to cause PRH in multi-ethnic populations without CF [36]. Given that structured exercise training can improve insulin sensitivity in adults with CF [37], in addition to quantifiable physical activity levels not being routinely monitored in our clinic, it is not possible to determine whether the improved $\dot{V}O_{2max}$ in the PRH group was a pathophysiological consequence, or a product of a more physically active lifestyle. Further research to investigate the association between insulin sensitivity, physical activity and aerobic fitness in people with CF would be useful in furthering our understanding of this phenomenon.

A strength of the present study was the use of a CPET protocol which has shown to produce a valid measurement of $\dot{V}O_{2max}$ in children, adolescents, and adults with mild to severe CF lung disease [22]. Notable limitations are that the retrospective nature of the data analysis meant the sample size of a heterogeneous cohort was relatively modest, the IGT group size was considerably

smaller and more descriptive physiologically relevant measurements were not conducted (i.e. continuous glucose monitoring as opposed to HbA1c). Indeed, investigating glycaemic control using HbA1c in people with CF is debated, as HbA1c analysis does not distinguish between variable bouts of hypo- and hyperglycaemia as opposed to time spent within an optimal range of blood glucose levels [30]. However, as yet, no alterative measure has been widely accepted in routine clinical practice. Furthermore, as the present study was cross-sectional this data only demonstrates an association and not a causal effect between dysglycaemia and aerobic fitness. Therefore, future prospective studies are needed to further investigate the clinical implications of these associations and whether they are a suitable outcome for interventional trials (e.g. impact of IVAB on glycaemic control and exercise capacity during a pulmonary exacerbation).

To conclude, in this study, CF-related dysglycaemia was associated with a significantly reduced aerobic fitness in adults with CF due to advanced CF lung disease in this population. Additionally, CFRD and IGT were associated with ventilatory dysfunction during exercise independent of lung function. The modulators of $\dot{V}O_{2max}$ in this cohort, including adults with mild to severe CF lung disease appear to be gender and BMI.

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CONFLICT OF INTERESTS

There are no conflict of interests to report.

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TABLES AND FIGURES

Table 1. Participant characteristics.

	NGT	IGT	CFRD	*p*-value	n^2
Sample size, *n*	19	8	19	-	-
Males, *n* (%)	11 (57.9)	4 (50.0)	11 (57.9)	-	-
Age, y	27.5 ± 7.6	23.4 ± 7.6	27.8 ± 6.9	0.34	0.05
Height, cm	168.7 ± 10.8	171.1 ± 14.6	169.4 ± 8.0	0.85	0.01
Body mass, kg	65.4 ± 11.5	61.6 ± 7.6	63.4 ± 12.9	0.72	0.02
BMI, $kg \cdot m^2$	23.0 ± 3.5	21.2 ± 2.6	22.0 ± 3.2	0.38	0.05
$FEV_{1,}$ % predicted[a]	**77.3 ± 19.4**	**52.1 ± 15.2***	**58.9 ± 17.5***	**<0.01**	**0.26**
	(29.9 – 105.7)	(36.4 – 75.4)	(26.8 – 95.9)	-	-
FVC, % predicted[a]	**89.4 ± 12.0**	**72.8 ± 7.1***	**75.0 ± 15.4***	**<0.01**	**0.26**
	(61.4 – 106.1)	(65.8 – 82.7)	(44.5 – 106.5)	-	-
Resting SpO_2, %	97 ± 2	96 ± 2	96 ± 2	0.60	0.03
CFTR genotype class, *n* (%)	-	-	-	-	-
Class I-III	17 (89.4)	8 (100.0)	19 (100.0)	-	-
Class IV-V	1 (5.3)	-	-	-	-
Unknown	1 (5.3)	-	-	-	-
P. aeruginosa infection, *n* (%)	11 (57.9)	4 (50.0)	15 (78.9)	-	-
Pancreatic insufficient, *n* (%)	11 (57.9)	8 (100.0)	19 (100.0)	-	-
FPG, $mmol \cdot L^{-1}$	4.7 ± 0.4	5.3 ± 0.9	4.0 ± 0.3[b]	0.39	0.07
2 h plasma [glucose], $mmol \cdot L^{-1}$	**4.3 ± 1.3**	**8.0 ± 2.7**	**15.0 ± 3.8[b]**	**<0.01**	**0.42**
	(2.7 – 7.4)	(4.2 – 10.4)	(11.3 – 18.8)	-	-
HbA1c, $mmol \cdot mol^{-1}$	**34.3 ± 3.8**	**39.7 ± 3.6***	**48.6 ± 15.6***	**<0.01**	**0.26**
	(27 – 43)	(32 – 48)	(33 – 100)	-	-
Time on IVAB, days	**10 ± 10**	**39 ± 20***	**27 ± 22***	**<0.01**	**0.27**
	(0 – 28)	(10 – 69)	(0 – 70)	-	-

Data are expressed as means ± standard deviation unless otherwise stated. * denotes a significant difference with the adult NGT group ($p < 0.05$). Range is provided in brackets for the variables obtaining statistical significance during ANOVA. [a] According to Global Lung Function Initiative 2012 reference values [21]; [b] glycaemic control assessments are not routinely conducted in people with established diabetes ('CFRD' $n = 4$). BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFRD, cystic fibrosis-related diabetes; FEV_1, forced expiratory volume in 1 s; FPG, fasting plasma [glucose]; FVC, forced vital capacity; HbA1c, glycated haemoglobin; IGT, impaired glucose tolerance; IVAB, intravenous antibiotics over 12 months; n^2, partial eta-squared;

NGT, normal glucose tolerance; *P. aeruginosa*, Pseudomonas aeruginosa; SpO_2, transcutaneous arterial oxygen saturation.

Table 2. Multiple linear regression model investigating the explained variance of maximal oxygen uptake ($\dot{V}O_{2max}$) by anthropometric, lung function and glycaemic control variables in adults with cystic fibrosis.

	$\dot{V}O_{2max}$ (mL·kg·min^{-1})		
	B	**SE**	***p*-value**
Gender, male vs. female	**-9.33**	**2.26**	**<0.01**
Age, y	-0.04	0.17	0.82
BMI, kg·m^2	**-1.28**	**0.41**	**<0.01**
$FEV_{1,}$ % predicted[a]	0.05	0.11	0.64
FVC, % predicted[a]	0.15	0.15	0.33
Pancreatic insufficient, no vs. yes	-1.53	3.70	0.68
IVAB, days	0.06	0.08	0.46
Dysglycaemia, no vs. yes[b]	-2.42	1.60	0.14
HbA1c, mmol·mol^{-1}	0.08	0.10	0.46

Data are expressed as the linear regression slope (*B*), standard error (SE) and p-value. [a] According to Global Lung Function Initiative 2012 reference values [21]; [b] Dysglycaemia accounts for adults with impaired glucose tolerance or cystic fibrosis-related diabetes. BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HbA1c, glycated haemoglobin; IVAB, intravenous antibiotics; SpO_2, transcutaneous arterial oxygen saturation.

Table 3. Pearson's correlation coefficients between maximal oxygen uptake ($\dot{V}O_{2max}$) and clinical variables in people with cystic fibrosis (CF), with and without CF-related diabetes (CFRD).

	Participants without CFRD (*n* = 27)		**Participants with CFRD (*n* = 19)**	
	$\dot{V}O_{2max}$ ($mL \cdot kg \cdot min^{-1}$)	$\dot{V}O_{2max}$ (% predicted)	$\dot{V}O_{2max}$ ($mL \cdot kg \cdot min^{-1}$)	$\dot{V}O_{2max}$ (% predicted)
Age, y	0.14	0.28	**-0.55***	-0.12
FEV_1, % predicted[a]	0.14	**0.43***	**0.48***	**0.54***
FVC, % predicted[a]	0.17	**0.44***	**0.47***	**0.49***
Resting SpO_2, %	0.01	-0.04	0.01	0.29
FPG, $mmol \cdot L^{-1}$	0.18	-0.03	-0.31[a]	-0.44[a]
2 h plasma [glucose], $mmol \cdot L^{-1}$	-0.13	**-0.42***	0.50[a]	0.63[a]
HbA1c, $mmol \cdot mol^{-1}$	0.17	-0.08	-0.34	-0.01
Time on IVAB, days	**-0.47**	**-0.41***	0.39	**0.45***

Data is presented as Pearson's correlation coefficient (*r*). * denotes a statistically significant correlation coefficient ($p < 0.05$). [a] Oral glucose tolerance testing was only conducted in 4 participants with CFRD during the study period. *N.b.* the 'Participants without CFRD' group contains adults with normal and impaired glucose tolerance. BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FPG, fasting plasma [glucose]; FVC, forced vital capacity; HbA1c, glycated haemoglobin; IVAB, intravenous antibiotics; SpO_2, transcutaneous arterial oxygen saturation.

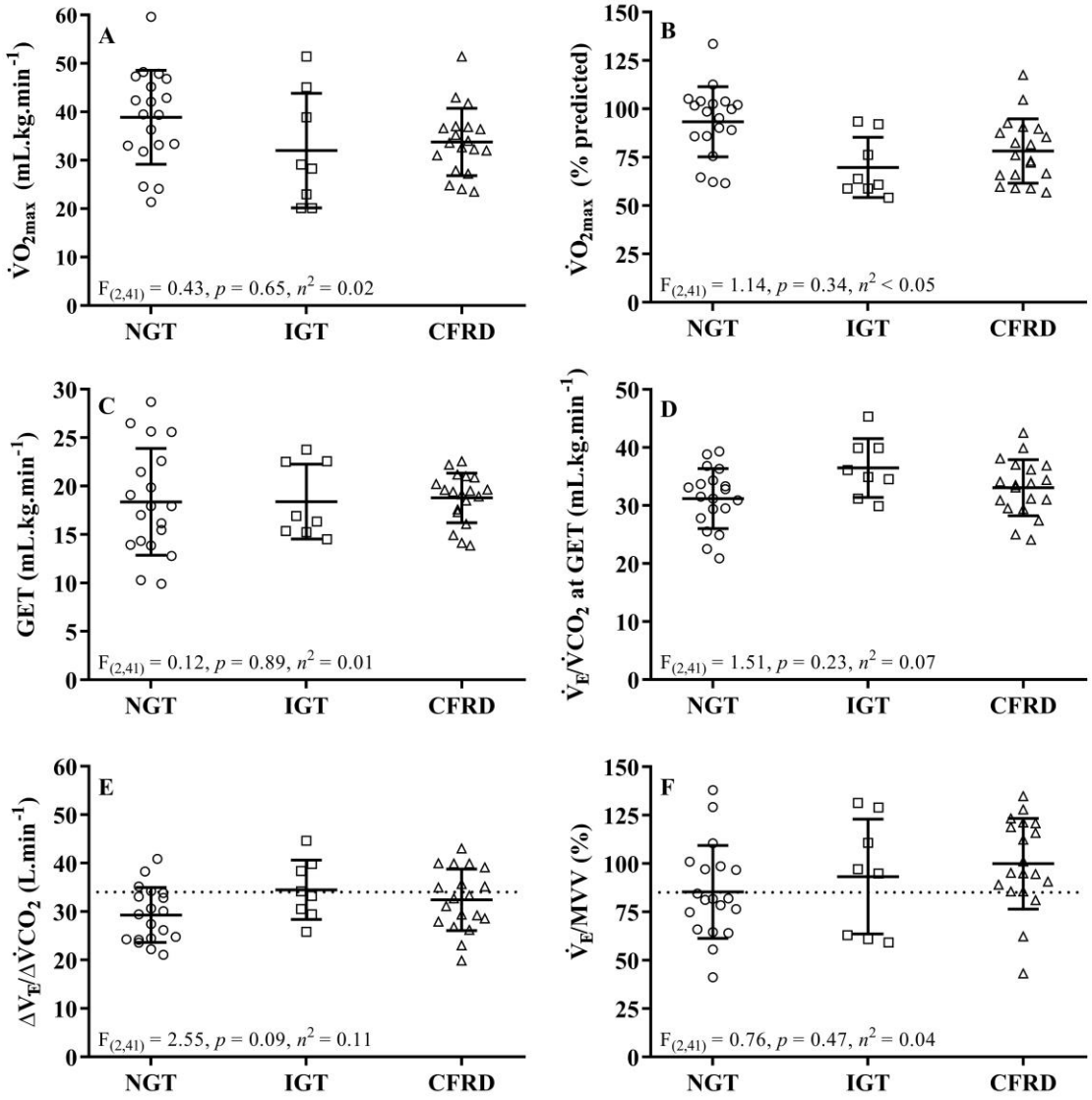

Figure 1. Parameters of aerobic fitness and ventilatory function during cardiopulmonary exercise testing in adults with cystic fibrosis (CF) and normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and CF-related diabetes (CFRD). Panels represent the following: *(A)* maximal oxygen uptake ($\dot{V}O_{2max}$) expressed relative to body mass (mL·kg·min^{-1}), *(B)* $\dot{V}O_{2max}$ as a percentage of normative values, *(C)* $\dot{V}O_2$ at gas exchange threshold (GET) expressed relative to body mass (mL·kg·min^{-1}), *(D)* GET as a percentage of $\dot{V}O_{2max}$, *(E)* ventilatory drive ($\Delta\dot{V}_E/\Delta\dot{V}CO_2$) and *(F)* minute ventilation ($\dot{V}_E$) expressed relative to predicted maximal voluntary ventilation (MVV). The statistics reported in this figure are those derived from analysis of covariance, where forced expiratory volume in 1 s and forced expiratory volume were included as covariates. *N.b.* the dotted line at 34 (Panel E) and 85% (Panel F) denotes the threshold for a ventilatory-perfusion mismatch and ventilatory limitation during CPET, respectively. n^2, partial eta-squared.

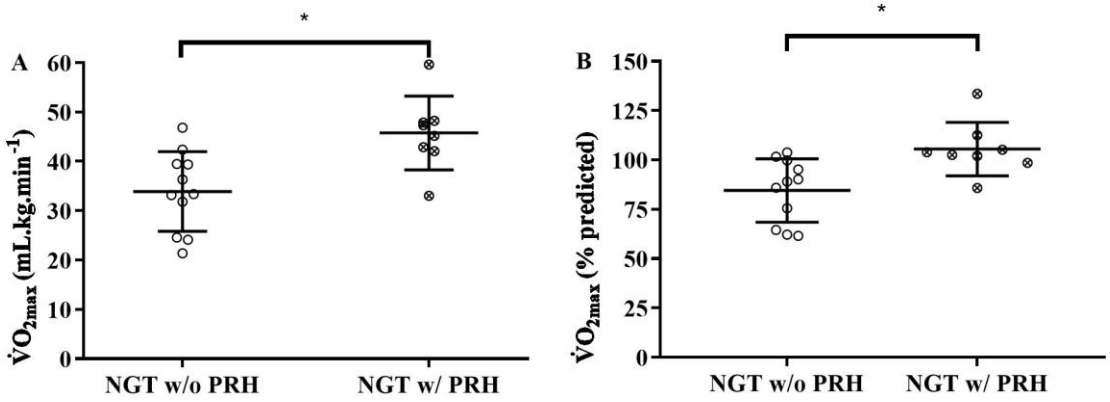

Figure 2. Maximal oxygen uptake ($\dot{V}O_{2max}$) in adults with cystic fibrosis and normal glucose tolerance (NGT), with or without post-reactive hypoglycaemia (PRH), during oral glucose tolerance testing. *(A)* Represents $\dot{V}O_{2max}$ expressed relative to body mass, and *(B)* $\dot{V}O_{2max}$ as a percentage of normative values. * denotes a significant difference between groups ($p < 0.05$).

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