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Skeletal muscle weakness, exercise tolerance and physical activity in adults with cystic fibrosis

T. Troosters*,#, D. Langer*,#, B. Vrijsen#,¶, J. Segers#, K. Wouters#, W. Janssens*, R. Gosselink*,#, M. Decramer*,# and L. Dupont¶

ABSTRACT: The aim of the present study was to investigate the prevalence of muscle weakness and the importance of physical inactivity in cystic fibrosis (CF), and its relationship to exercise tolerance and muscle strength.

Exercise tolerance, skeletal and respiratory muscle strength were studied in a group of 64 adults with CF (age 26±8 yrs, FEV_{1} % predicted 65±19) and in 20 age-matched controls. Physical activity (PA) was assessed in 20 patients and all controls.

Quadriceps muscle weakness was present in 56% of the patients. Peak oxygen uptake and 6-min walking distance were below normal in 89 and 75% of patients, respectively. Respiratory muscle strength was normal. The differences remained after correcting for PA. Quadriceps force was correlated to the 6-min walking distance but not to peak oxygen uptake. ''Mild'' PA (>3 metabolic equivalents (METS)) and the number of steps overlapped with controls, but CF patients had less moderate PA (>4.8 METS). Moderate PA was related to peak oxygen uptake and quadriceps force.

Skeletal muscle weakness and exercise intolerance are prevalent in cystic fibrosis. Physical inactivity is a factor significantly contributing to exercise tolerance and skeletal muscle force in adults with cystic fibrosis, but these impairments are in excess to that expected from physical inactivity only.

KEYWORDS: Adults, cystic fibrosis, exercise tolerance, physical activity, skeletal muscle

The prognosis of cystic fibrosis (CF) has continued to improve over the last decades. As a result, the number of adult patients needing to be managed is growing. One aspect of the care of this chronic condition is the management of the systemic consequences of the disease, including exercise intolerance and reduced bone mineral density [1]. Exercise intolerance is a clear hallmark of CF [2] but the factors leading to exercise intolerance remain poorly understood. DODD *et al.* [3] suggested that pulmonary factors were not limiting peak exercise capacity in patients with moderate CF. DODD *et al.* [4] also showed that bronchodilators enhanced lung function, but were unsuccessful in improving exercise tolerance, again suggesting that respiratory factors are not the only limiting factor in CF. Skeletal muscle dysfunction has been suggested as a factor contributing to reduced exercise tolerance in children with CF [5, 6]. This has not been studied in detail in adult CF patients [7].

It has been suggested that patients with CF may suffer from skeletal muscle weakness. However, these reports are from relatively small cohorts [8] or patients with severe CF [9, 10]. A recent larger study including 33 patients with milder disease suggested that peripheral muscle force was not significantly reduced [11]. In order to resolve the discrepancies in the current literature a larger study is needed. Several factors may be related to impaired muscle force. Systemic inflammation, oxidative stress [12], nutritional imbalance and electrolyte disturbances [13] may contribute to skeletal muscle weakness in CF. Inactivity is another factor that may contribute to both skeletal muscle weakness and exercise intolerance [14]. Although it is tempting to assume that adults with CF are inactive there are no data to support this. Children with mild CF have been shown to be more physically active compared with their control peers [15]. It is important to know whether in CF, as in other chronic diseases,

AFFILIATIONS
*Respiratory Rehabilitation and Respiratory Division, and
¶Cystic Fibrosis Centre, Respiratory Division, University Hospital Leuven, and
#Faculty of Kinesiology and Rehabilitation Sciences, Dept of Rehabilitation Sciences, Katholieke Universiteit Leuven, Leuven, Belgium.

CORRESPONDENCE
T. Troosters
Respiratory Rehabilitation and Respiratory Division
UZ Gasthuisberg
Herestraat 49
B-3000 Leuven
Belgium
Fax: 32 16347126
E-mail: Thierry.Troosters@med.kuleuven.be

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inactivity begins at an early stage of the disease and contributes to further reduction in exercise tolerance and skeletal muscle dysfunction.

The present study investigated the prevalence of skeletal muscle weakness and exercise intolerance in adult patients with CF. Furthermore, the present authors aimed to assess the prevalence of physical inactivity in these patients and its relationship with skeletal muscle force and exercise tolerance.

METHODS

Subjects and design

A convenience sample of 64 patients (35 male) with CF (71% of the total number of adult patients in follow-up at the University Hospital Leuven, Leuven, Belgium) and 20 age-matched control subjects (11 male) were recruited. Patients were recruited during a planned, annual control visit to the CF centre of the University Hospital Leuven. Patients were free from other conditions that could interfere with the testing procedures (*e.g.* orthopaedic, cardiac or neurological conditions). Patients with an exacerbation in the 6 weeks prior to the study, patients on the waiting list for lung transplantation and those who had undergone lung transplantation were excluded from the study. The 2-day visits were part of the normal clinical routine in all registered patients with CF at the University Hospital Leuven. Skeletal and respiratory muscle strength was assessed. A maximal incremental exercise test was conducted and two 6-min walking distance (6MWD) tests were performed. The healthy controls and 20 CF patients were equipped with a physical activity (PA) monitor. Their habitual physical activities were assessed for a period of 5–7 days. The selection of the patients for the activity monitoring in the present study was based on the patient's ability to easily return the activity monitor *i.e.* living in the area or near the investigators, allowing them to pick-up the activity monitor. No other selection criteria were used.

Healthy control subjects were free of chronic diseases and volunteered to participate in the study. Eight of the subjects were students of the faculty of Kinesiology and Rehabilitation Sciences (University Hospital Leuven), four were students at other faculties and eight were employed. The study was approved by the ethics committee of the University Hospital Leuven and all subjects gave informed consent to participate in the study.

Methods

Measurement of spirometry and maximal voluntary ventilation was performed according to the guidelines of the European Respiratory Society. Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) are expressed as percentage of the normal values, as proposed by QUANJER *et al.* [16]. Respiratory muscle strength was assessed from total lung capacity for expiration (maximal expiratory pressure; $P_{E,max}$) or residual volume for inspiratory respiratory pressure (maximal inspiratory pressure; $P_{I,max}$) using the technique proposed by BLACK and HYATT [17]. An electronic pressure transducer was used (MicroRPM; Micromedical, Kent, UK). The normal values used were those proposed by ROCHESTER and ARORA [18]. Hand-grip strength was measured using a hydraulic hand dynamometer (Jamar Preston, Jackson, MI, USA) with the arm in a neutral position and the elbow flexed at 90°. Normal values were those proposed by MATTHIOWETZ *et al.* [19]. Isometric quadriceps force was assessed with the subject seated on a dynamometer (Cybex Norm; Enraf Nonius, Delft, the Netherlands), with the back straight and a 90° hip flexion; knee flexion was 60°. Normal values had been previously developed [20].

A maximal incremental exercise test was conducted. After a period of rest, the patients were asked to cycle at a fixed pace (55–65 cycles·min^{-1}). After 3 min of unloaded cycling, work rate was increased by 20 watts·min^{-1}. The test was continued until exhaustion and subjects were encouraged throughout the test. Ventilation, oxygen uptake (V'_{O_2}, expressed in mL·min^{-1}·kg^{-1}), respiratory exchange ratio, transcutaneous oxygen saturation and maximal cardiac frequency (fCmax) were collected for further analysis. Peak V'_{O_2} ($V'_{O_2,peak}$) was also expressed as a percentage of the predicted value [21].

Patients and healthy volunteers also completed two encouraged 6MWD tests in a 50-m hospital corridor [22]. The maximal distance covered is reported for further analysis. Results for age range are expressed as a percentage of the predicted value according to the study by GIBBONS *et al.* [23].

Activity monitor

PA was assessed in a subset of 20 representative patients and in all healthy controls. PA was assessed when patients were at home for at least five full days. Data are reported as the average of 5 days.

Subjects wore a multi-sensor armband (Sensewear; BodyMedia, Pittsburgh, PA, USA) for 5–7 days. The portable armband contained two accelerometers, a galvanic skin response sensor, a heat flux sensor, a skin temperature sensor and a near-body ambient temperature sensor from which the data were stored minute by minute. Using specific software these variables, as well as body weight, height, handedness and smoking status (smoker or nonsmoker) were used to estimate the intensity of PA, expressed in metabolic equivalents (METS). The armbands estimation of free-living energy expenditure has recently been validated in 50 subjects against doubly labelled water [24]. It is positioned on the upper right arm (on the triceps and at mid-humerus point). The armband was only removed for bathing or showering. Patients were also instructed to wear the armband during the night. The outcome obtained from the armband was the time spent in PA at different intensities. The time (in min) spent with an energy expenditure of >3 METS was considered ''mild'' activity, time spent at >4.8 METS was considered ''moderate'' activity and activities with an energy expenditure of >7.2 METS were considered ''vigorous'' activity, as suggested by the US Department of Health and Human Services [25]. Mild activity is typically associated to walking at normal walking speed and carrying out light household work. Moderate activity requires brisk walking or cycling and is required to maintain fitness. Vigorous activity may yield significant training effects when applied for a sufficient length of time and at an appropriate training frequency [26]. Finally, the number of steps was also measured. When the number of steps was <7,500 steps·day^{-1} the level of activity was considered too low [27]. The error range was estimated in a small pilot study of eight subjects, comparing the armband with manual counting of steps at a

slow (0.89 ± 0.5 m·s^{-1}) and a fast speed (1.97 ± 0.2 m·s^{-1}). The error was 3% (95% confidence interval (CI) -9–3%) and -4% (95% CI -16–7%), respectively.

Statistical analysis

Data are presented as mean±SD, unless specified otherwise. Patients and healthy controls were compared using an unpaired t-test. Differences between groups are reported as mean difference and 95% CI. For the healthy control subjects the lower limit of normal was calculated as the value above which 95% of the control values were situated.

To investigate whether skeletal muscle force is related to exercise tolerance in CF, a stepwise multiple regression analysis was performed with sex, age, lung function, anthropometry, respiratory and peripheral muscle force as potential independent variables.

Since activity monitoring data were not normally distributed the comparison of the PA data was performed using a Mann–Whitney test in order to investigate the differences between patients and controls. These data are reported as median (interquartile range).

Pearson and Spearman correlations were calculated to investigate associations. Partial correlations were calculated to investigate whether any relationship existed between $V'_{O_2,peak}$ and 6MWD on the one hand and PA on the other, after correcting for anthropometric variables and muscle force. To investigate whether skeletal muscle strength and exercise tolerance were different between patients and controls, after correcting for PA and other potential covariates, the least square means were computed for the dependent variables using a generalised linear models procedure. Dependent variables were *a priori* corrected for age, weight, height, sex and PA level (number of steps and time spent in moderate PA). A p-value <0.05 was considered as statistically significant.

RESULTS

Patients were well matched with control subjects in terms of age and sex (table 1). As expected, CF patients were slightly lighter and smaller than the controls. The 20 CF patients in whom PA level was assessed were representative for the complete sample in terms of age and anthropometric characteristics and muscle strength. However, the subgroup tended to have a better FEV1 and 6MWD ($p=0.12$ and $p=0.07$ *versus* total group) and had significantly better peak exercise tolerance ($p=0.03$).

Muscle force

Peripheral muscle force was significantly lower in patients with CF compared with healthy controls. Quadriceps force was 24 (95% CI 16–33)% predicted lower in patients compared with controls and was below the lower limit of normal in 56% of the patients. Similarly, hand-grip force was 17 (95% CI 9–25)% pred lower in patients compared with controls and was below the lower limit of normal in 56% of the patients. Figure 1 illustrates the quadriceps and hand-grip force. There was no difference in muscle weakness between male and female patients. Quadriceps force was unrelated to lung function in CF (R= -0.07 and -0.06 for FEV1 and FVC, respectively; both $p>0.58$). Figure 2 illustrates the absence of a relationship between quadriceps force and FEV1 in patients. A poor, but statistically significant relationship was found between hand-grip strength and lung function impairment (FEV1: $R=0.25$, $p=0.05$; FVC: $R=0.31$, $p=0.02$). Respiratory muscle function was not reduced in CF. On average, the $P_{I,max}$ was 4 (95% CI -9–17)% pred lower and $P_{E,max}$ was 10 (95% CI -1–22)% pred lower in patients compared with controls. These differences were not statistically significant.

TABLE 1 Baseline characteristics of patients with cystic fibrosis (CF) and control subjects

Characteristics	Male		Female	
	CF	Control	CF	Control
Subjects n	35	11	29	9
Age yrs	25±6	24±3	27±9	26±6
Weight kg	64±13	76±9	56±10	61±8
Height cm	175±9	183±6	164±8	169±7
FEV1 % pred	64±19	101±16	66±20	108±5
FVC % pred	83±13	118±10	83±19	113±12
$P_{I,max}$ % pred	91±23	98±16	108±30	108±21
$P_{E,max}$ % pred	95±23	101±15	103±22	119±22

Data are presented as mean± SD, unless otherwise stated. FEV1: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity; $P_{I,max}$: maximal inspiratory pressure; $P_{E,max}$: maximal expiratory pressure.

Exercise tolerance

Exercise tolerance was assessed in all CF patients and was reduced in most patients (table 2). $V'_{O_2,peak}$, expressed as % pred value, was below the lower 5% percentile of the controls in 89% of the subjects. The 6MWD was abnormally low in 75% of the patients. The relationship of $V'_{O_2,peak}$ and 6MWD with lung function in patients and controls is shown in figure 3.

In the multiple regression analysis, conducted in the 64 CF patients, 68% of the variance in $V'_{O_2,peak}$ (% pred) was explained by FEV1 expressed as % pred (partial $R^2=0.57$, $p<0.001$), sex (partial $R^2=0.05$, $p=0.005$) and body weight (partial $R^2=0.07$, $p=0.002$). Peripheral and respiratory muscle force did not contribute to the model.

In total, 59% of the variance in the 6MWD was explained by sex ($R^2=0.30$, $p<0.001$), FVC ($R^2=0.11$, $p<0.002$), quadriceps force ($R^2=0.08$, $p<0.005$), age ($R^2=0.07$, $p<0.004$) and body weight ($R^2=0.02$, $p<0.09$). When the 6MWD was expressed as % pred, only FVC ($R^2=0.17$, $p<0.008$) and quadriceps force ($R^2=0.10$, $p<0.007$) remained in the model.

Physical activities and function

The number of steps and PA at mild intensity were not different in patients compared with healthy subjects (table 3 and fig. 4). In total, 15% of the healthy controls and 35% of CF patients had <7,500 steps·day^{-1} ($p=0.14$). Activities with at least moderate intensity were reduced in patients with CF ($p=0.03$; fig. 4), similarly, there was a trend for less activities at vigorous intensity (CF 4.2 (0.63–9.7) min *versus* 9.5 (3.7–18.6) min; $p=0.09$).

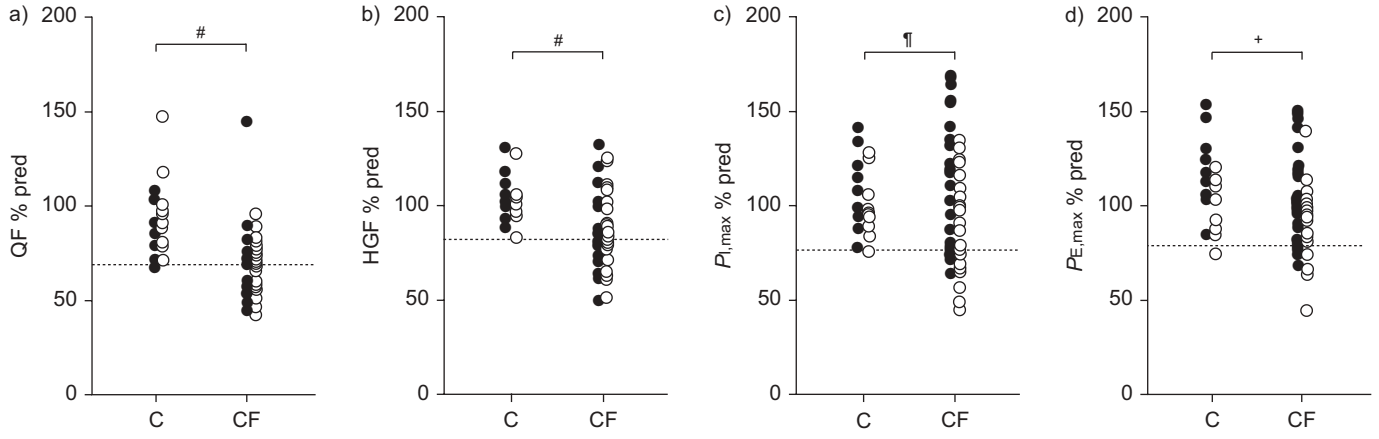

FIGURE 1. Skeletal and respiratory muscle function. a) Quadriceps force (QF), b) hand-grip force (HGF), c) maximal inspiratory ($P_{I,max}$) and d) maximal expiratory pressure ($P_{E,max}$) in male (○) and female (●) control subjects (C) and patients with cystic fibrosis (CF). % pred: % predicted. ·····: lower limit of normal. #: $p<0.0001$; ¶: $p=0.43$; +: $p=0.14$.

Single correlation analysis was conducted in CF patients. There was only a trend for a relationship between the number of steps per day and lung function (FEV1: $R=0.39$, $p=0.08$; FVC: $R=0.42$, $p=0.07$). Quadriceps force was related to the time spent in moderate ($R=0.48$, $p=0.03$) and hard ($R=0.52$, $p=0.02$) PA, but not to the time spent in mild PA or the number of steps. PA was moderately related to $V'_{O_2,peak}$, expressed as % pred (moderate PA: $R=0.56$; vigorous PA: $R=0.52$, both $p<0.02$; steps per day: $R=0.47$, $p<0.05$; fig. 5). After correcting for the previously mentioned covariates explaining variance in $V'_{O_2,peak}$ (FEV1, weight, sex), PA only tended to explain further variance in $V'_{O_2,peak}$ ($R^2=0.16$, $p=0.10$). FEV1 remained the most significant factor explaining variance in $V'_{O_2,peak}$ ($R^2=0.47$, $p=0.002$). The 6MWD was not strongly related to the PA outcomes. This reached statistical significance only for the time spent in vigorous PA ($R=0.45$, $p=0.04$). After correcting for the previously mentioned covariates, no additional variance in the 6MWD was explained by PA levels.

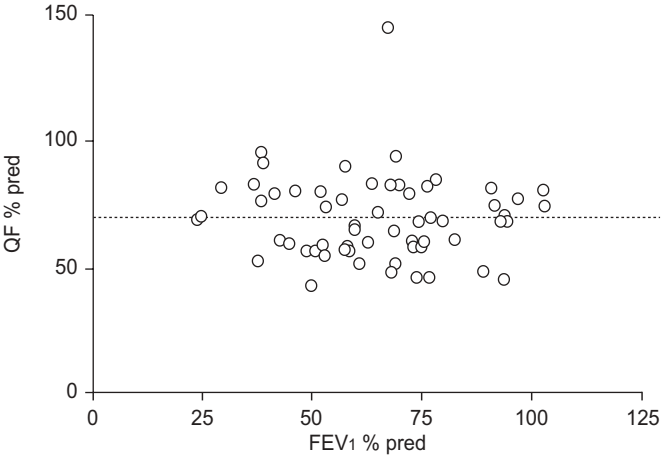

FIGURE 2. Relationship between lung function impairment (as assessed by forced expiratory volume in one second (FEV1)) and quadriceps force (QF) in patients with cystic fibrosis. % pred: % predicted. ·····: lower limit of normal obtained from healthy controls.

Significant differences remained between the healthy control group and patients with CF after correcting for the covariates physical activity and anthropometric differences. Using a least squares approach with covariates age, weight, height, sex and physical activity (number of steps per day and time spent in moderately intense physical activity), 6MWD was 78 m less (11% pred, $p<0.002$), quadriceps force 50 Nm less (22% pred, $p<0.001$) and $V'_{O_2,peak}$ was 30% pred lower (13.1 $mL \cdot min^{-1} \cdot kg^{-1}$, $p<0.001$) in patients compared with controls.

DISCUSSION

The most important finding of the present study is the prevalence of skeletal muscle weakness and exercise intolerance in adult CF patients with moderate lung function impairment. Although peak and functional exercise tolerance were impaired in almost all patients, only 35% of patients could be classified as too inactive. Although PA at mild intensity was still normal in CF, physical activities above moderate intensity were significantly reduced in CF compared with controls. PA levels were identified as a significant, but rather modest contributor to quadriceps weakness and exercise intolerance in CF. In the present study, the additional variance in exercise tolerance after correcting for lung function and anthropometric variables was limited. Interestingly, despite the modest relationship between PA and exercise tolerance and skeletal muscle force, significant differences remained between patients and controls after correcting for these covariates. This indicates that other factors contribute to the reduced skeletal muscle strength and impaired exercise tolerance in CF.

This is the largest controlled study to investigate the prevalence of peripheral and respiratory muscle weakness in CF. Consistent with other studies, the present authors did not find respiratory muscle weakness in CF patients [28]. Quadriceps force was significantly reduced and was abnormal in ~60% of the study cohort. The reduction in quadriceps force was similar to that reported in a study by ELKIN *et al.* [10], which investigated patients of similar age with an average FEV1 of 52% pred. In that cohort the patients had an isometric

TABLE 2 Skeletal muscle force and exercise capacity in patients with cystic fibrosis (CF) and control subjects

	Control	CF	Mean difference (95% CI)	p-value
Subjects n	20	64		
Quad % pred	93±19	69±16	25 (16–33)	<0.001
Hand % pred	102±13	84±18	17 (9–25)	<0.001
6MWD m	833±93	702±82	131 (87–174)	<0.001
6MWD % pred	107±11	91±9	16 (12–21)	<0.001
W_{max} W	259±60	155±57	104 (74–134)	<0.001
$V'_{O_2,peak}$ mL·min^{-1}·kg^{-1}	48±8.1	30.2±9.7	18 (13–23)	<0.001
$V'_{O_2,peak}$ % pred	112±16	71±18	41 (32–50)	<0.001
RER	1.21±0.09	1.14±0.08	0.07 (0.03–0.11)	0.001
f_{Cmax} beats·min^{-1}	187±7.7	176±16	12 (4–19)	0.002
f_{Cmax} % pred	96±5	90±7.2	5 (2–9)	0.003
$V'_{E,max}$ L·min^{-1}	113±29	80±22	33 (21–45)	<0.001
$V'_{E,max}$ % MVV	73±18	84±14	-11 (-20– -4)	0.003
V'_{O_2}·f_C^{-1} mL	17.0±4.1	10.3±3.3	7 (5–9)	<0.001
V'_E·$V'_{O_2}^{-1}$	36.1±6.4	46.0±8.5	-10 (-14– -5)	<0.001
V'_E·$V'_{CO_2}^{-1}$	29.6±4.0	40.4±7.5	-11 (-14– -7)	<0.001

Data are presented as mean±SD, unless otherwise stated. CI: confidence interval; quad: quadriceps force; % pred: % predicted; hand: hand-grip strength; 6MWD: 6-min walking distance; W_{max}: maximal work rate; $V'_{O_2,peak}$: peak oxygen uptake; RER: respiratory exchange ratio; f_{Cmax}: maximal cardiac frequency; $V'_{E,max}$: maximal minute ventilation; MVV: maximal voluntary ventilation; V'_{O_2}·f_C^{-1}: oxygen pulse; V'_E·$V'_{O_2}^{-1}$: ventilatory equivalent for oxygen; V'_E·$V'_{CO_2}^{-1}$: ventilatory equivalent for carbon dioxide.

quadriceps force of 65% of their controls. In the current study patients reached only 69% of the controls' quadriceps force. Taking into account the lower body weight in the CF patients (by expressing muscle force as % pred) the patients were 24% pred weaker than the controls. The difference in body weight is inherent to studies of adult CF patients [10]. The current data contrast with another recent study of patients with mild CF [11]. It can only be speculated as to why both populations are different, but in the latter study [11] the authors reported that their patients were engaged in regular physical training two to three times per week. This was surely not the case in the present study patients.

In the present study, it was found that quadriceps force was a significant contributor to the variance in the 6MWD, but did not contribute to maximal exercise capacity (as measured by $V'_{O_2,peak}$). In absolute values, quadriceps force was significantly related to $V'_{O_2,peak}$ ($R=0.55$, $p<0.0001$). This is in agreement with other studies which have suggested that lean body mass [7] or skeletal muscle strength [5] are predictors of $V'_{O_2,peak}$. However, this relationship may reflect covariates of both factors such as age, sex and body weight (influencing both quadriceps force and $V'_{O_2,peak}$). Both quadriceps force and $V'_{O_2,peak}$ were expressed as % pred of the normal value. This corrects force for the factors age, weight and sex. An important predictor of peak exercise tolerance in the present study is lung function impairment. Even after correcting for physical activity levels, lung function remained a significant predictor of $V'_{O_2,peak}$. Interestingly, and in agreement with findings in chronic obstructive pulmonary disease, lung function was only a poor determinant of functional exercise tolerance, as assessed by the 6MWD [29].

This is only the second study in which physical activity levels were assessed in adults with CF. Subtle, but important

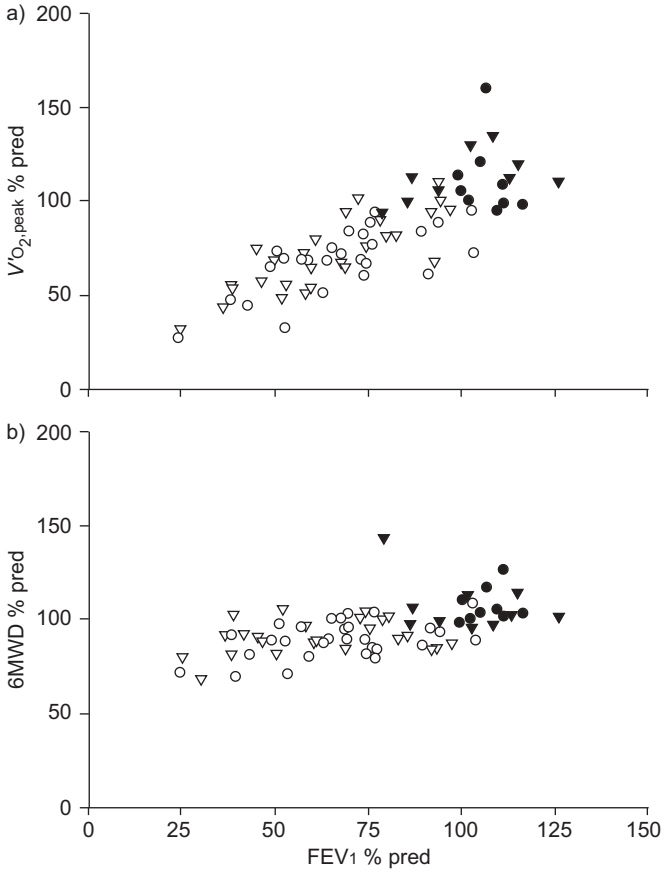

FIGURE 3. Relationship between forced expiratory volume in one second (FEV_1) and a) peak oxygen uptake ($V'_{O_2,peak}$) and b) 6-min walking distance (6MWD) in healthy subjects (●, ▼) and patients with cystic fibrosis (○, ▽). ▽, ▼: male subjects; ○, ●: female subjects. % pred: % predicted.

TABLE 3 Characteristics of the subgroup of 20 patients with cystic fibrosis (CF) and 20 healthy controls

	Control	CF	p-value
Age yrs	24±5	25±5	0.64
FEV1 % pred	104±11	72±18	<0.001
$V'_{O_2,peak}$ mL·min^{-1}·kg^{-1}	47±7.4	36±8.2#	<0.001
Steps·day^{-1}	10281 (7928–12360)	9398 (6317–12970)	0.37
Moderate intensity activities min·day^{-1}	34.5 (20.6–53.8)	14.8 (8.6–36.8)	0.03

Data are presented as mean±SD or mean difference (95% confidence interval), unless otherwise stated. FEV1: forced expiratory volume in one second; % pred: % predicted; $V'_{O_2,peak}$: peak oxygen uptake. #: significant difference to the complete group (n=64, p=0.03).

differences were noted in these relatively mild patients. A recent study of HEBENSTREIT *et al.* [14] measured physical activities in CF in an uncontrolled study using an accelerometer that provided counts per min. The current authors classified PA as mild, moderate or vigorous PAs. From figure 4 it is clear that there is a significant overlap in mild activities between healthy subjects and patients with CF. Adults with CF seem to engage in a relatively normal amount of PAs at mild intensities (such as walking on the level at a normal pace). However, differences appear between patients and healthy age-matched subjects in activities at moderate and more intense levels. This is important since it is generally acknowledged that PAs at moderate intensity have an important long-term protective effect on health [30]. It is noteworthy, and clinically relevant, that a significant minority (35%) of the study patients would qualify as having a PA level that is below the level needed to maintain health [27]. These subjects may need extra attention to enhance PA levels since an inactive life style is associated with significant morbidity [30], such as osteoporosis [1] and insulin resistance. Nevertheless there is arguably a large overlap between patients and control subjects in any of the PA outcomes.

It is of note that statistically significant, but modest (R^2=0.32) correlations were observed between PAs and $V'_{O_2,peak}$. After correcting for other covariates, including lung function, only 16% of additional variance was explained by PA (p=0.10). Part of the explanation for the modest relationship between PA and $V'_{O_2,peak}$ can surely be the day to day variability of PA. However, assessment of 2 days of PA has previously been shown to be enough for this type of analysis [31]. In the present study, PA was assessed for 5–7 days. Clearly other factors, such as lung function impairment, play an important role in explaining variance in $V'_{O_2,peak}$ and a large portion of the variability remains unexplained in current models. In order to assess causality, the effect of interventions aimed at enhancing PA should be studied.

The present study also reports that the time spent above moderate intensity was related to quadriceps force. Altogether, these findings support the guideline of the American College of Sports Medicine, that moderate PA levels should be recommended to maintain physical fitness (both exercise tolerance and skeletal muscle force) [32].

An important finding of the present study is that $V'_{O_2,peak}$, 6MWD and quadriceps force remained significantly different between patients and controls after correcting for inactivity as a covariate. This indicates that factors other than daily PAs or lung function impairment do contribute to the reduced exercise tolerance and muscle force. The present study focused on the role of physical inactivity, but several factors not investigated in the present study may contribute to the reduced exercise capacity. These factors may be related to pulmonary or systemic inflammation, oxidative stress, the number of exacerbations in patients with CF, gas exchange

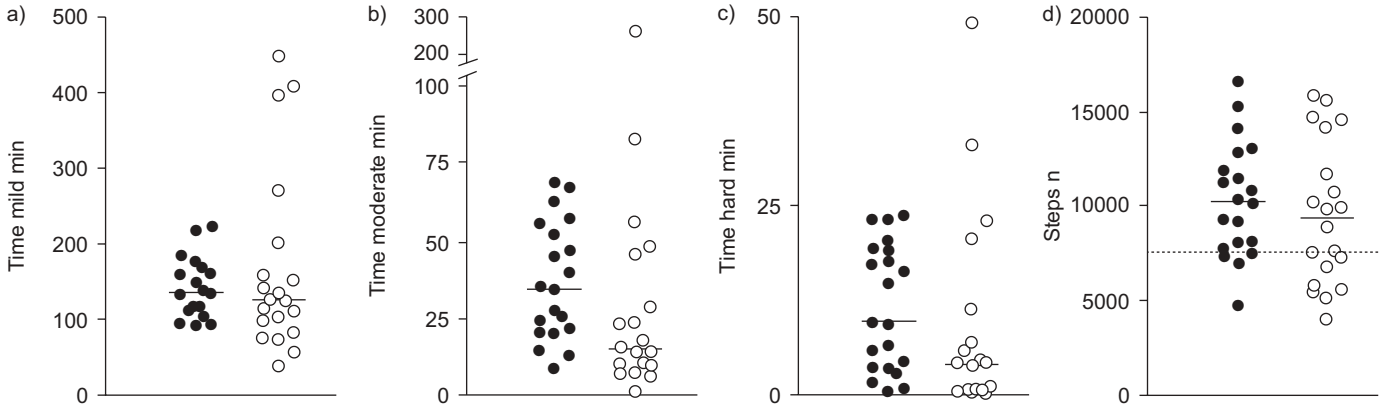

FIGURE 4. Physical activities above the threshold of a) mild activity (>3 metabolic equivalents (METS)), b) moderate activity (>4.8 METS) or c) hard activities (>7.2 METS), as well as d) the number of steps per day in healthy subjects (●) and 20 cystic fibrosis patients (○).

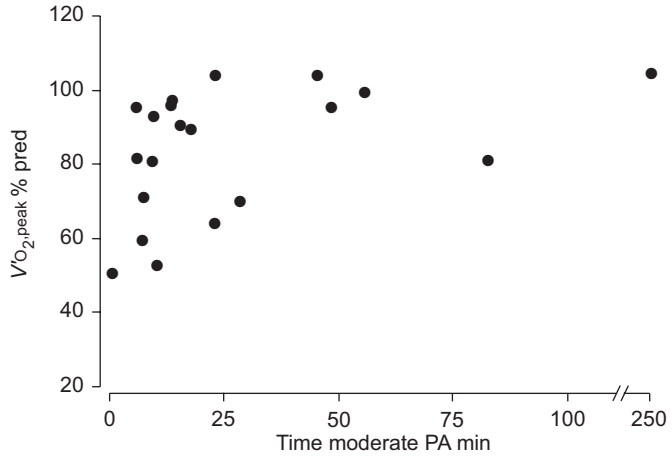

FIGURE 5. Relationship between the time spent in moderate physical activities (PA) and peak oxygen uptake ($V'O_{2,peak}$) in patients with cystic fibrosis. % pred: % predicted.

abnormalities, nutritional impairment or electrolyte disturbances. For example, systemic inflammation was shown to be associated with other systemic consequences of CF, such as reduced bone mineral density [33, 34]. The current data demonstrate that in patients with CF, peak exercise tolerance is relatively more reduced than activities of daily living. By consequence, normal PA does occur closer to the maximum capacity of CF patients. Recently, IONESCU *et al.* [35] showed that in CF, systemic interleukin-6 and tumour necrosis factor-α were increased at rest and further increased after exercise of ~5 min at ~3.1 METS, which mimics mild activities in daily life. Exacerbations may be another factor relevant to the development of muscle weakness [36]. In chronic obstructive pulmonary disease acute exacerbations have also been associated with the reduction in skeletal muscle force [37, 38]. Further research in larger patient groups is needed to enhance the understanding of reduced skeletal muscle function in CF. The present study indicates that inactivity should be considered as a covariate in such studies.

In conclusion, skeletal muscle weakness and exercise intolerance are prevalent in adult patients with cystic fibrosis. Careful analysis of the patients' physical activity revealed that the time spent in physical activity of mild intensity was essentially normal in cystic fibrosis, but patients spent less time in moderately intense physical activity. Physical activity is related to exercise intolerance and skeletal muscle weakness, but the impairment in skeletal muscle dysfunction and exercise tolerance is in excess to that expected from inactivity only. Larger studies may be needed to confirm the results of this single centre study.

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