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Skeletal muscle weakness, exercise tolerance and Physical activity in adults with Cystic Fibrosis.

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Abstract

The aim of this study was to investigate the prevalence of muscle weakness and the importance of physical inactivity in CF and its relation to exercise tolerance and muscle strength.

We studied exercise tolerance, skeletal and respiratory muscle strength in a large group of adults with CF (n=64, age 26±8, FEV1 65±19%pred) 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 consumption and six minute walking distance was 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 six minute walking distance (partial R2 0.08 $p<0.01$) but not to peak oxygen consumption. 'Mild' PA (>3 Metabolic equivalents, METS) and the number of steps overlapped with controls, but patients had less moderate PA (above 4.8METS). Moderate PA was related to VO_2peak ($R=0.56$; $p<0.01$) and Quadriceps force ($R=0.48$; $p=0.03$).

Conclusion: Skeletal muscle weakness and exercise intolerance are prevalent in CF. 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.

Introduction

The prognosis of cystic fibrosis (CF) has continued to improve in the last decades. As a consequence the number of adult patients that needs to be managed is growing. An 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 clearly a hallmark of cystic fibrosis[2] but the factors leading to exercise intolerance remain poorly understood. Dodd and coworkers suggested that pulmonary factors were not limiting peak exercise capacity in patients with moderate CF[3]. These investigators 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[4]. Skeletal muscle dysfunction has been suggested as a factor contributing to reduced exercise tolerance in children[5;6] with CF. In adult patients this has not been studied in much detail[7].

It has been suggested that patients with cystic fibrosis may suffer from skeletal muscle weakness. However these reports come from relatively small cohorts[8] or patients with severe cystic fibrosis[9;10]. A recent larger study including thirty-three patients with milder disease suggested that peripheral muscle force was not significantly reduced[11]. In order to resolve the discrepancies present 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 which 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 supporting this. Children with mild CF were even shown to be more physically active compared to their control peers[15]. It is important to know whether in CF, like in other chronic diseases, inactivity sets on 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 cystic fibrosis. Furthermore we 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 cystic fibrosis (71% of the total number of adult patients in follow-up in our hospital) and 20 age matched control subjects (11 male) were recruited in the study. Patients were recruited during a planned annual control visit to the cystic fibrosis centre of the University Hospital Leuven. Patients were –apart from their CF- free of other conditions that could interfere with the testing procedures (e.g. orthopaedic, cardiac or neurological conditions). Patients with an exacerbation in the six weeks before the study, patients on the waiting list for lung transplantation and those after lung transplantation were excluded from the study. The two day visits were part of the normal clinical routine in all registered patients with cystic fibrosis (CF) at our centre. Skeletal and respiratory muscle strength was assessed. A maximal incremental exercise test was conducted and two six minute walking tests were performed. All healthy controls and 20 CF patients were equipped with a physical activity monitor. Their habitual physical activities were assessed for a period of five to seven days. The selection of the patients for the activity monitoring in the present study was based on the patients' ability to easily return the activity monitor (living in the neighbourhood, or near one of the investigators, allowing to pick-up of 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, 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 (MVV) were done according to the guidelines of the European Respiratory Society. Forced expiratory volume and vital capacity are expressed as percentage of the normal values proposed by Quanjer[16]. Respiratory muscle strength was assessed from total lung capacity (for expiratory; PEmax) or residual volume (for inspiratory respiratory pressure PImax) using the technique proposed by Black and Hyatt[17]. An electronic pressure transducer was used (MicroRPM, Micromedical, Kent, UK). Normal values were those proposed by Rochester and Arora[18]. Hand grip strength was measured using a hydraulic hand dynamometer (Jamar Preston, Jackson, MI, US) with the arm in a neutral position and the elbow flexed 90°. Normal values were those proposed by Matthiowetz[19]. Isometric quadriceps force was assessed with the subject seated on a dynamometer (Cybex Norm, Enraf Nonius, Delft, The Netherlands), the back straight and with 90° hip flexion. Knee flexion was 60°. Normal values were previously developed in our laboratory[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 three minutes of unloaded cycling, work rate was increased by 20 watts.min^{-1}. The test

was continued until exhaustion and subjects were encouraged during the test. Peak exercise data: Ventilation, Oxygen consumption (VO_2peak, expressed in $ml.min^{-1}.kg^{-1}$), respiratory exchange ratio (RER) Transcutaneous oxygen saturation (StcO2) and maximal heart rate (HRmax) were collected for further analysis. Peak oxygen consumption was also expressed as a percentage of the predicted value[21].

Patients and healthy volunteers also completed two encouraged six minute walking tests in a 50m hospital corridor[22]. The maximal distance covered is reported for further analysis. Results are also expressed as a percentage of the predicted value as proposed for subjects in the age range of the present study by Gibbons[23].

Activity monitor

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

Subjects wore a multi-sensor armband (Sensewear, BodyMedia, Pittsburgh, US) for five to seven days. The portable armband contains 2 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 are stored minute by minute. Using specific software (Sensewear 6.1 Pro) these variables, as well as body weight, height, handedness, and smoking status (smoker or non-

smoker) are used to estimate the intensity of physical activity, 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 removed only for bathing or showering. Patients were instructed to wear the armband also during the night. Outcomes obtained from the armband were the time spent in physical activity at different intensities. The time (in minutes) spent with an energy expenditure larger than 3 Metabolic equivalents (METS) was considered 'mild' activity, time spent above 4.8METS was considered 'moderate' activity and activities with an energy expenditure >7.2METS were considered 'vigorous' activity, as suggested by the Surgeon General[25]. Mild activity is typically associated to walking at normal walking speed and 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 sufficiently long and at an appropriate training frequency[26]. Lastly also the number of steps is measured. When the number of steps was below 7500 steps.day^{-1} the level of activity was considered too low[27].The error range was estimated in a small pilot study (n=8) comparing the armband with manual counting of steps at slow ($0.89\pm0.5 m.s^{-1}$) and fast speed ($1.97\pm0.2 m.s^{-1}$). The error was -3%, 95%CI -9 to 3% and -4%, 95%CI -16 to 7% respectively.

Statistical analysis

Statistical analysis was performed with the SAS statistical package (v9.1, SAS Institute, Cary, NC, USA). Data are presented as mean and standard deviation, unless specified otherwise. Patients and healthy controls were compared using an unpaired t-test. Differences between groups are reported as mean difference and 95% confidence interval (95%CI). For the healthy control subjects the lower limit of normal (LLN) 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 gender, 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 physical activity data was done using a Mann-Whitney test in order to investigate the differences between patients and controls. These data are reported as median and inter-quartile range.

Pearson and Spearman correlations were calculated to investigate associations. Partial correlations were calculated to investigate whether any relation existed between peak oxygen consumption and six minute walking distance on the one hand and physical activity 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 physical activity and other potential covariates the least square means were

computed for the dependent variables using a generalized linear models procedure. Dependent variables were a priori corrected for age, weight, height, gender and physical activity level (number of steps and time spent in moderate physical activity). A priori a p-value less than 0.05 was considered as statistically significant.

Results

Patients were well matched with control subjects in terms of age and gender (**Table 1**). As expected, patients were slightly lighter and smaller than the controls. The 20 CF patients in whom physical activity level was assessed were representative for the complete sample in terms of age and anthropometric characteristics and muscle strength. The sub-group, however, tended to have a better FEV1 and 6MWD (p=0.12 and p=0.07 vs. 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 to healthy controls. Quadriceps force was 24 [95%CI 16-33] % predicted lower in patients compared to controls and was below the lower limit of normal in 56% of the patients. Similarly, hand grip force was 17 [95%CI 9-25] % predicted lower in patients compared to 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 with FEV1, R=-0.06 with FVC, both p>0.58). **Figure 2** illustrates the absence of a relation between Quadriceps force and FEV1 in patients. A poor, but statistically significant relation was found between hand grip strength and lung function impairment (R=0.25, p=0.05 with FEV1, R=0.31, p=0.02 with FVC). Respiratory muscle function was not reduced in CF. On the average, PImax was 4 [95%CI -9

to 17] % predicted lower and PEmax was 10 [95%CI -1 to 22] %predicted lower in patients compared to controls. These differences were not statistically significant.

Exercise tolerance

Exercise tolerance was assessed in all CF patients and was reduced in most patients (**Table 2**). VO_2peak, expressed in % of the predicted value was below the p5 of the controls in 89% of the subjects. The 6MWD was abnormally low in 75% of the patients. The relation of peak VO2 and 6MWD with lung function in patients and controls are shown in **Figure 3**.

In multiple regression analysis, conducted in the 64 CF patients, 68% of the variance in VO_2peak (%predicted) was explained by FEV1 expressed as percentage of the predicted value (partial R^2=0.57, p<0.001), gender (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.

Fifty nine percent of the variance in the 6MWD was explained by gender (R^2=0.30, p<0.001), FVC expressed as percentage of the predicted value (R^2=0.11, p<0.002), quadriceps force expressed as a percentage of the predicted value (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 a percentage of the predicted value, only FVC (%pred, R^2=0.17, p<0.008 and quadriceps force (%pred R^2=0.10, p<0.007) remained in the model.

Physical activities and function

The number of steps and physical activity at 'mild' intensity were not different in patients compared to healthy subjects **(Table 3 and Figure 4)**. Fifteen percent of the healthy controls and 35% of CF patients had less than 7500 steps per day (p=0.14). Activities with at least moderate intensity were reduced in patients with CF (p=0.03, **Figure 4**), similarly, there was a trend for less activities at 'vigorous' intensity (CF 4.2 [0.63-9.7] min vs. 9.5 [3.7-18.6] min p=0.09).

Single correlation analysis was conducted in CF patients. There was only a trend for a relation between the number of steps per day and lung function (R=0.39 with FEV1, p=0.08 and R=0.42 with FVC, 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) physical activity (PA), but not to the time spent in mild PA or the number of steps. Physical activity was moderately related to peak oxygen consumption, expressed as percentage of the predicted value (moderate PA: R=0.56 **(Figure 5)**, vigorous PA: R=0.52, all p<0.02, and steps per day R=0.47, p<0.05). After correcting for the above mentioned covariates explaining variance in peak VO2 (FEV1, weight, gender), physical activity only tended to explain further variance in peak VO2 (R^2 0.16, p=0.10). Lung function (FEV1) remained the most significant factor explaining variance in peak VO2 (R^2 0.47, p=0.002). The six minute walking distance was not strongly related to the physical activity outcomes. This reached

statistical significance only for the time spent in vigorous PA (R=0.45, p=0.04). After correcting for the above mentioned co-variates, no additional variance in the 6MWD was explained by physical activity levels.

Significant differences remained between the healthy control group and patients with cystic fibrosis after correcting for the covariates physical activity and anthropometric differences. Using a least squares approach with covariates age, weight, height, gender and physical activity (number of steps per day and time spent in moderately intense physical activity) 6MWD was 78m (11% of the predicted value, $p<0.002$) less, Quadriceps force 50Nm (22% predicted, $p<0.001$) less and peak oxygen consumption was 30% predicted (13.1ml.min^{-1}.kg^{-1} , $p<0.001$) lower in patients compared to controls.

Discussion

The most important finding of the present study is the prevalence of skeletal muscle weakness and exercise intolerance, in adult patients with Cystic Fibrosis with moderate lung function impairment. Although peak and functional exercise tolerance were impaired in almost all patients, only 35% of patients can be classified as too inactive. Although physical activities at 'mild' intensity were still normal in CF, physical activities above moderate intensity were significantly reduced in CF, compared to controls. Physical activity 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 relations between physical activity and exercise tolerance and skeletal muscle force, significant differences remained between patients and controls after correcting for these co-variates. This indicates that other factors, contribute to the reduced skeletal muscle strength and impaired exercise tolerance in cystic fibrosis.

This is the largest controlled study to investigate the prevalence of peripheral and respiratory muscle weakness in CF. Consistent with other reports, we did not find respiratory muscle weakness in CF patients[28]. Quadriceps force was significantly reduced and was abnormal in approximately 60% of our cohort. The reduction in quadriceps force was similar to that reported in a study of Elkin et al,

investigating patients of similar age with an average FEV1 of 52%predicted[10]. In their cohort the patients had an isometric quadriceps force of 65% of their controls. In our study patients reached only 69% of the controls' quadriceps force. Taking into account the lower body weight in the patients (by expressing muscle force as % of the predicted value) the patients were 24% predicted weaker than the controls. The difference in body weight is inherent to studies of adult CF patients[10]. Our data contrast with another recent study of patients with mild CF[11]. We can only speculate 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 on two to three times per week. This was surely not the case in our patients (see below).

In the present study we found that quadriceps force was a significant contributor to the variance in the six minute walking test, but did not contribute to maximal exercise capacity (as measured by VO_2peak). In absolute values quadriceps force was significantly related to VO_2peak ($R=0.55$, $p<0.0001$). This is in agreement with other authors who suggested that lean body mass[7] or skeletal muscle strength[5] are predictors of VO_2peak. However this relation may rather reflect covariates of both factors such as age, gender and body weight (influencing both QF and VO_2peak). We expressed quadriceps force and peak VO2 as percentage of the predicted normal value. This corrects force for the factors age, weight and gender. An important predictor of peak exercise tolerance is lung function impairment in the present study. Even after correcting

for physical activity levels, lung function remained a significant predictor of peak oxygen consumption. Interestingly and in agreement with findings in COPD, 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 are assessed in adults with cystic fibrosis. Subtle, but important 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 provides counts/min. We classified physical activity as 'mild', 'moderate' or 'vigorous' physical activities. 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 physical activities 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 physical activities 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 our patients would qualify as having a physical activity level that is below the level needed to maintain health[27]. These subjects may need extra attention to enhance physical activity levels since an inactive life style is associated with significant morbidity[30] such as osteoporosis[1] and insulin

resistance. Nevertheless there is arguably large overlap between patients and control subjects in any of the physical activity outcomes.

It is of note that statistically significant, but modest (R^2 0.32) correlations were observed between physical activities and VO_2peak. After correcting for other co-variates, including lung function only 16% of additional variance was explained by physical activity (p=0.10). Part of the explanation for the modest relation between physical activity and peak oxygen consumption can surely be the day to day variability of physical activity. However, assessment of two days of physical activity has previously been shown to be enough for this type of analysis[31]. In the present study physical activity was assessed for five to seven days. Clearly other factors, such as the lung function impairment are playing an important role in explaining variance in peak VO2 and a large portion of the variability remains unexplained in current models. In order to assess causality the effect of interventions aiming at enhancing physical activity should be studied.

The present study also reports that the time above 'moderate' intensity was related to quadriceps force. Altogether, these findings support the guideline of the American College of Sports Medicine that moderate physical activity 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 peak oxygen consumption, six minute walking distance and quadriceps force, remained significantly different between patients and controls after correcting for inactivity as a covariate. This

indicates that factors other than daily physical activities 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 abnormalities, nutritional impairment or electrolyte disturbances. Systemic inflammation, for example showed to be associated to other systemic consequences of CF, such as reduced bone mineral density[33;34]. Our data demonstrate that in patients with CF, peak exercise tolerance is relatively more reduced than activities of daily living. By consequence, normal physical activity does occur closer to the maximum capacity of CF patients. Recently Ionescu et al. showed that in CF, systemic IL-6 and TNF-α were increased at rest and further increased after exercise of approximately 5 minutes at approximately 3.1 METS, which mimics mild activities in daily life[35]. Exacerbations, may be another factor, relevant to the development of muscle weakness[36]. In COPD acute exacerbations have also been associated to the reduction in skeletal muscle force[37;38]. Further research in larger patient groups is needed to enhance our 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 CF, 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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		Male		Female	
		CF (n=35)	**Ctrl (n=11)**	**CF (n=29)**	**Ctrl (n=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
PImax	%pred	91 ± 23	98 ± 16	108 ± 30	108 ± 21
PEmax	%pred	95 ± 23	101 ± 15	103 ± 22	119 ± 22

Table 1 Baseline characteristics of male and female patients (CF) and control subjects (Ctrl). Besides anthropometric variables, forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), maximal inspiratory pressure (PImax) and maximal expiratory pressure (PEmax) are given as percentage of the predicted value.

		Ctrl n=20	CF n=64	Difference Mean [95%CI]	p-value
Quadr	(%pred)	93 ± 19	69 ± 16	25 [16 to 33]	<0.001
Hand	(%pred)	102 ± 13	84 ± 18	17 [9 to 25]	<0.001
6MWD	(m)	833 ± 93	702 ± 82	131 [87 to 174]	<0.001
	(% pred)	107 ± 11	91 ± 9	16 [12 to 21]	<0.001
Wmax	(Watts)	259 ± 60	155 ± 57	104 [74 to 134]	<0.001
VO_2peak	($ml.min^{-1}.kg^{-1}$)	48 ± 8.1	30.2 ± 9.7	18 [13 to 23]	<0.001
	(%pred)	112 ± 16	71 ± 18	41 [32 to 50]	<0.001
RER		1.21 ± 0.09	1.14 ± 0.08	0.07 [0.03 to 0.11]	=0.001
HRmax	(min^{-1})	187 ± 7.7	176 ± 16	12 [4 to 19]	0.002
	(%pred)	96 ± 5	90 ± 7.2	5 [2 to 9]	0.003
VEmax	($L.min^{-1}$)	113 ± 29	80 ± 22	33 [21 to 45]	<0.001
	(% MVV)	73 ± 18	84 ± 14	-11 [-20 to -4]	=0.003
$VO_2.HR^{-1}$	(ml)	17.0 ± 4.1	10.3 ± 3.3	7 [5 to 9]	<0.001
$VE.VO_2^{-1}$		36.1 ± 6.4	46.0 ± 8.5	-10 [-14 to -5]	<0.001
$VE.VCO_2^{-1}$		29.6 ± 4.0	40.4 ± 7.5	-11 [-14 to -7]	<0.001

Table 2 Skeletal muscle force (Quadriceps force: Quadr and Hand grip strength: Hand) in % of the predicted value and exercise capacity in patients with Cystic Fibrosis (CF) and control subjects. The six minute walking distance (6MWD) is given in meters (m) and % of the predicted normal value, maximal work rate in

watts (Wmax), peak oxygen consumption (VO_2peak), respiratory exchange ratio (RER) and maximal heart rate (HRmax) is given in beats mer minute and as a percentage of the age predicted maximum. Maximal ventilation is given in $L.min^{-1}$ and as a percentage of the maximal voluntary ventilation (%MVV). Oxygen pulse ($VO2.HR^{-1}$) and ventilatory equivalents for oxygen ($VE.VO_2^{-1}$) and for carbon dioxide ($VE.VCO_2^{-1}$) complete the exercise test results. Means and standard deviations for both groups are displayed, as well as the difference between groups and the 95% confidence interval of the mean difference. In addition the p-value is given.

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		Ctrl n=20	CF n=20	p-value
Age	(yrs)	24 ± 5	25 ± 5	0.64
FEV1	(%pred)	104 ± 11	72 ± 18	<0.001
VO_2peak	($ml.min^{-1}.kg^{-1}$)	47 ± 7.4	36 ± 8.2‡	<0.001
Steps	($n.day^{-1}$)	10281 [7928-12360]	9398 [6317-12970]	0.37
$Time_{Mod}$	(min day^{-1})	34.5 [20.6-53.8]	14.8 [8.6-36.8]	0.03

Table 3 Characteristics of the subgroup of 20 CF patients and healthy controls. ‡ indicates a significant difference to the complete group (n=64; p=0.03). Steps per day and time spent in activities with at least moderate intensity ($Time_{Mod}$). The p-value is given for the comparison of healthy controls versus the CF patients.

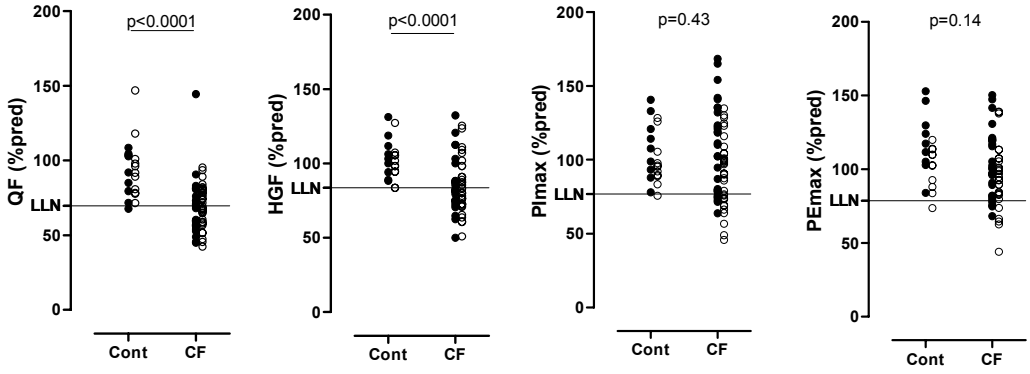

Figure 1 Skeletal and respiratory muscle function in male (open symbols) and female (closed symbols) control subjects (cont) and patients with cystic fibrosis (CF). Quadriceps force (QF), Hand grip strength (HGF), maximal inspiratory (PImax) and expiratory (PEmax) respiratory muscle force are given, all as a percentage of their respective predicted values. The lower limit of normal (LLN) is indicated with the dashed line.

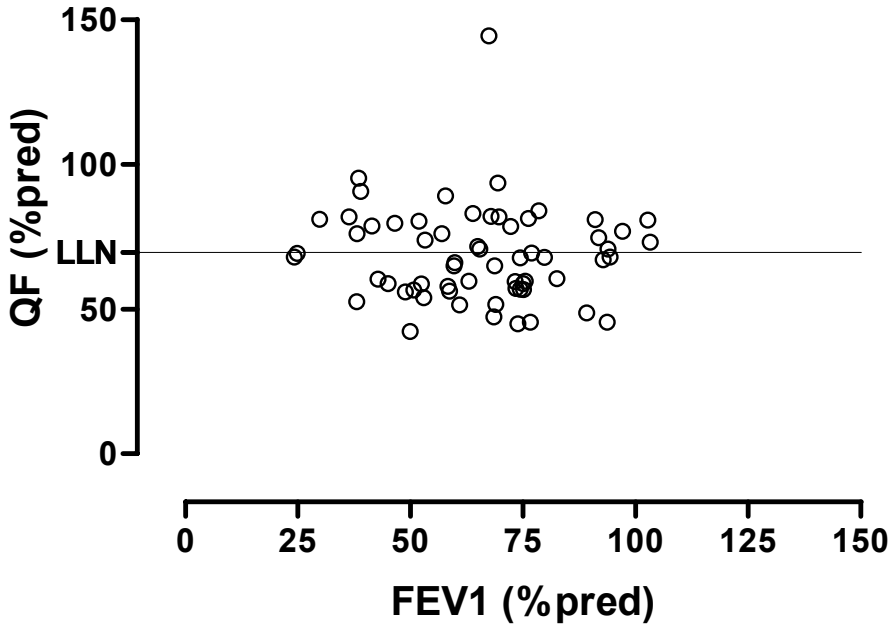

Figure 2 Relation between lung function impairment (FEV1) and quadriceps force (QF) in patients with CF. Both values are given as percentage of the predicted value (%pred). The lower limit of normal (LLN, obtained from the healthy controls) is indicated with the dashed line.

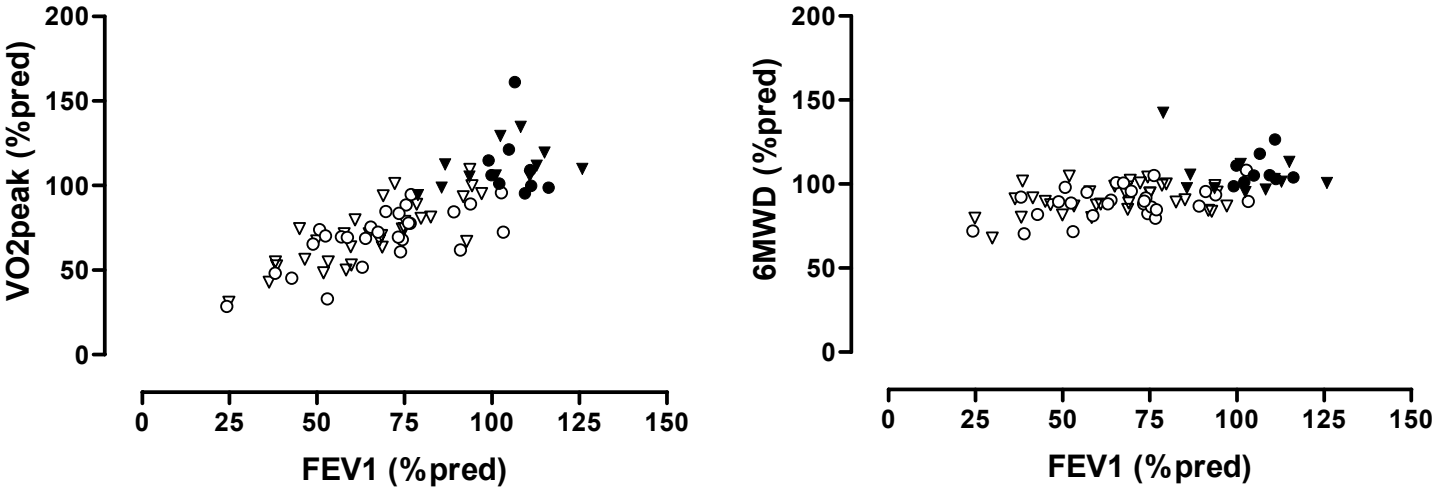

Figure 3 Relation between lung function (FEV1) and peak oxygen consumption (VO2, left panel) and six minute walking test (6MWD, right panel) in healthy subjects (closed symbols) and patients with Cystic Fibrosis (open symbols). Male subjects are displayed in triangles, female subjects as dots.

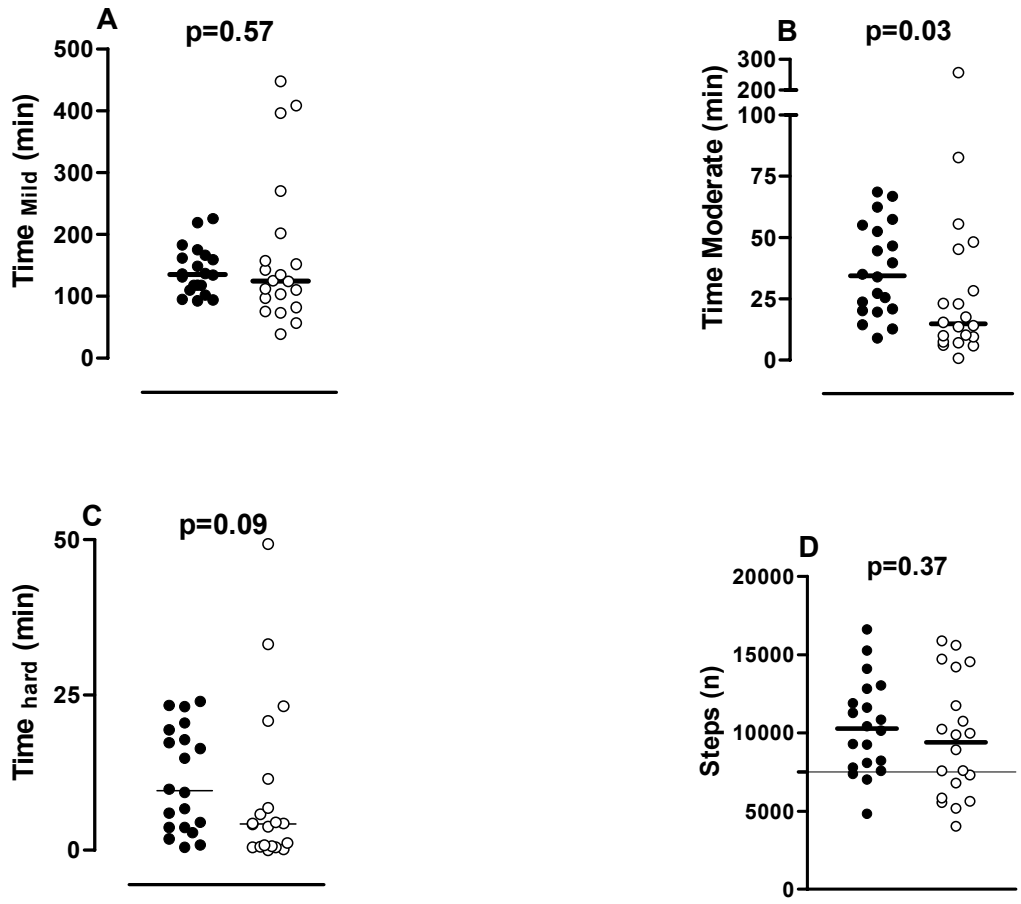

Figure 4 Physical activity levels in healthy subjects (closed symbols) and 20 CF patients (open symbols). Physical activities above the threshold of mild activity (>3METS, panel A), moderate (>4.8METS, panel B) or hard activities (>7.2METS, panel C) as well as the number of steps per day (panel D) are given.

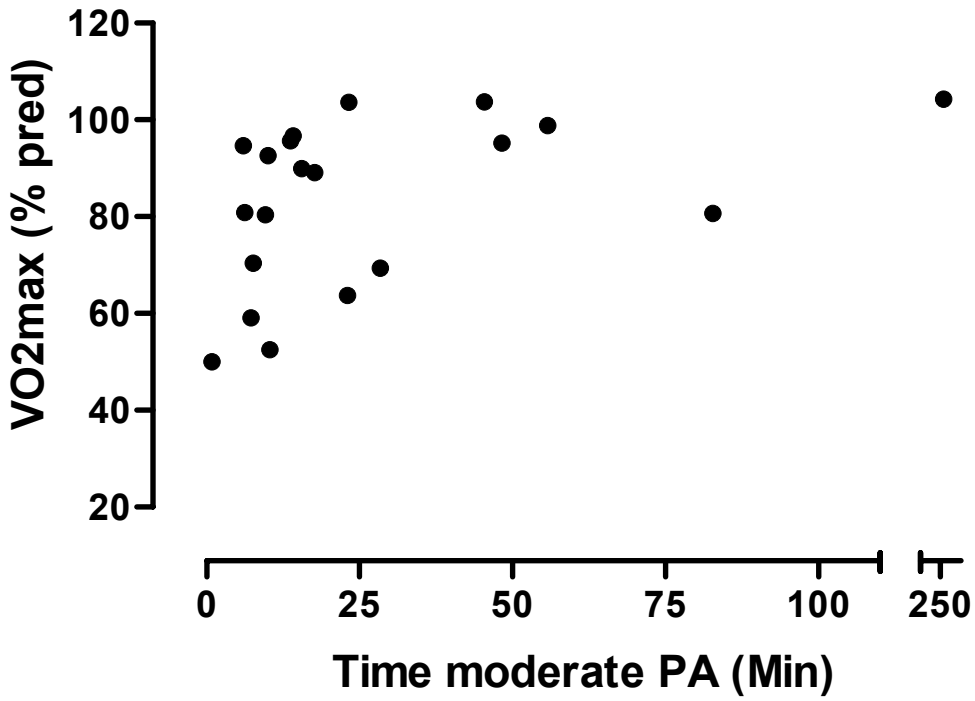

Figure 5 Relation between the time spent in moderate physical activities and peak oxygen consumption in patients with cystic fibrosis.