

Physical activity is independently related to aerobic capacity in cystic fibrosis

Helge Hebestreit¹, Stephanie Kieser¹, Susanne Rüdiger¹, Thomas Schenk¹, Sibylle Junge²,

Alexandra Hebestreit¹, Manfred Ballmann², Hans-Georg Posselt³, Susi Kriemler⁴

¹University Children's Hospital, Julius-Maximilians-Universität Würzburg, Germany;

²Pediatric Department, Medizinische Hochschule Hannover, Germany; ³Pediatric Department, Johann Wolfgang Goethe Universität, Frankfurt, Germany; and ⁴Exercise Physiology, Swiss Federal Institute of Technology and University of Zurich, Switzerland

Corresponding author: Prof. Dr. Helge Hebestreit

Universitäts-Kinderklinik

Josef-Schneider-Str. 2

97080 Würzburg

Germany

Tel.: +49 931 201 27728

FAX: +49 931 201 27242

Email: hebestreit@mail.uni-wuerzburg.de

Short title: Predictors of physical performance in CF

ABSTRACT (Word count 194)

It is unclear whether a relationship between physical activity (PA) and peak oxygen uptake (VO_2 peak) exists in cystic fibrosis (CF) and, if so, whether the relationship reflects a direct effect or is mediated by the effects of confounding variables such as pulmonary or muscle function. The objective of this study was, therefore, to determine the relationship between PA and VO_2 peak in CF while adjusting for possible influences of confounding factors.

We studied 36 female and 35 male patients with CF from Germany and Switzerland (12-40 yrs., FEV1 25-107%predicted). A Wingate test was employed to measure muscle power. PA was monitored for 7 days using the MTI/CSA 7164 accelerometer and expressed in two ways, average daily accelerometer count (ADAC) and time spent in moderate to vigorous PA (MVPA). VO_2 peak was determined during an incremental cycle exercise test to volitional fatigue.

PA was positively related to VO_2 peak. In a multiple linear regression analysis, height, gender, FEV1, muscle power, and ADAC (additionally explained variance 2.5%) or time spent in MVPA (additionally explained variance 3.7%) were identified as independent predictors of VO_2 peak.

In conclusion, high levels of PA in addition to good muscular and pulmonary functions are associated with a high aerobic capacity in CF.

Key words: activities of daily living, lung function, muscular exercise, fitness

INTRODUCTION

For patients with cystic fibrosis (CF), physical fitness is important in many aspects. First, patients with a high aerobic capacity have a higher life expectancy [1]. Second, aerobic capacity correlates with quality of life measures [2], and changes in the former are associated with changes in the latter [3]. And finally, in adults with CF, professional achievements are associated with physical fitness [4].

Peak oxygen uptake (VO_{2peak}), a measure of aerobic exercise capacity, increased with physical training in some studies on patients with CF [3,5,6]. It could, thus, be assumed that the level of habitual physical activity (PA) in an individual with CF influences his or her VO_{2peak} . However, some exercise intervention programs where physical activity was intentionally increased have failed to raise fitness levels [7,8]. Furthermore, the only study examining the relationship between physical activity and VO_{2peak} in CF found no correlation between the reported time spent in vigorous activities and VO_{2peak} in 30 patients aged 7 to 17 years [9]. Only in a subgroup of 10 patients with the lowest lung function ($FEV_1 < 80\%$), an association between vigorous physical activity and VO_{2peak} was observed. Since impaired lung function (and related factors such as frequency of pulmonary infections) may limit VO_{2peak} as well as physical activities [10-16], it is not clear whether the reported association between the two reflects a true cause-effect relationship or just the limitation of both by impaired lung function.

Like lung function, body composition and muscle power are related to VO_{2peak} in CF [15,16] and all might be positively affected by physical activity and regular exercise [3, 17,18]. A positive relationship between physical activity and VO_{2peak} in CF – if it should exist - might thus be mediated by an effect of physical activity on body composition, muscle mass, and muscle power and may not reflect a direct effect on VO_{2peak} itself.

The objective of this study was to describe the relationship between physical activity and VO_{2peak} in a large group of patients with CF, first without and then after controlling for

the effects of possible confounding factors such as anthropometric variables, age, gender, lung function, and muscle power. We hypothesized that physical activity would be related to VO_2peak in a large, heterogeneous group of patients but that no correlation would be observed when controlling for the effects of body size and composition, lung function, and short-term muscle power.

MATERIALS AND METHODS

Study Subjects

Patients diagnosed with CF and aged 12 years and older were recruited from CF-centers in Germany (Frankfurt, Hannover, Würzburg; n=37), and Switzerland (Basel, Bern Zurich; n=34). Patients' characteristics are summarized in Table 1.

Patients were stable at the time of the study and those with medical problems precluding maximal exercise testing were excluded. The study protocol was approved by the Ethics committees of all participating centers and written consent was obtained for each subject.

Study Design and Methods

After familiarization with procedures, height and body mass were determined, in light exercise clothing without shoes and skinfold thicknesses were measured as described by Lohman et al. [19]. Percent body fat (%BF) was calculated from skinfold thickness, using the equations provided by Slaughter et al. [20] for patients younger than 16 years, and the equations published by Durnin & Wormersley [21] for older patients. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were determined by standard spirometry (Masterscreen body, Jaeger, Würzburg, Germany) and expressed as %predicted [22].

Each patient completed a Wingate test on a calibrated mechanically braked cycle ergometer [23]. In all German centers, the identical Monark 834 E Ergomedic ergometer (Varberg, Sweden) was employed. In Switzerland, all testing was performed at one location in Zurich using a Fleisch ergometer (Metabo, Switzerland). For each patient, braking force was calculated from body mass using existing equations [24] and modified up to 10% depending on the performance in two short practice runs. The reason for this adjustment was to identify a braking force that would elicit the highest total mechanical work (TMW) during the 30-s test. TMW generated during the Wingate test was chosen as indicator of muscle power.

After at least 30 min of rest, subjects completed a continuous incremental cycling task to volitional fatigue [25]. Work rate was increased every minute by 15 to 20 Watts, depending on patient's height and physical fitness. All German patients were tested using the identical calibrated Monark 834 E cycle ergometer and metabolic cart (CPX/D, MedGraphics, St Paul, MN, USA). All testing of the Swiss patients employed an electronically braked ergometer (Ergoline 800c, Pilger, St. Gallen, Switzerland) and a Quark B2 metabolic cart (Cosmed, Rome, Italy). Both metabolic carts were calibrated before each exercise test with two gases of known concentrations (21% O₂, 79% N₂; 12% O₂, 5% CO₂, 81% N₂). Stability of the O₂- and CO₂-sensors was verified after each test. Maximal oxygen uptake (VO_{2peak}) was determined as highest VO₂ over 30 s during the test and normalized for body weight. VO_{2peak} was also expressed as a percentage of predicted [26]. Oxygen saturation (SpO₂) was monitored during the exercise test using pulse oximetry (Nellcor Reflectance oxygen sensor RS10, Nellcor Puritan Bennet Inc., Pleasanton, CA, USA).

Physical activity was monitored for 7 days using the MTI/CSA 7164 accelerometer (MTI Health Services, Fort Walton Beach, FL). Periods of 60 min or more with zero readings were excluded from analysis. All subjects completed at least 5 days of recordings with at least 10 hours of valid data per day. Activity was expressed in two ways: Average accelerometer count per day as an unmodified, measured variable and daily time spent in moderate and vigorous

physical activities (MVPA). Since there are no validation studies for the MTI/CSA 7164 or any other accelerometer in patients with cystic fibrosis, time spent in MVPA was somewhat arbitrarily defined as the average number of minutes per day with a recording >1000 counts \cdot min $^{-1}$. In healthy subjects, a value of 191 counts \cdot min $^{-1}$ was reported for the MTI/CSA 7164 as cut-off point distinguishing between light and moderate activities, if a variety of activities were included in the validation [27]. If only walking and jogging are employed for the validation, cut-offs around 2000 counts \cdot min $^{-1}$ have been published [27,28]. Since a considerable amount but not all activities of our patients included walking/jogging/running, the cut-off was set to 1000 counts \cdot min $^{-1}$.

Data analysis

To analyze the relationship between physical activity (average accelerometer counts per day and time spent in MVPA) and VO_2 peak (ml \cdot min $^{-1}\cdot$ kg $^{-1}$ and %predicted), linear regression analyses were performed and correlation coefficients were computed.

The regression analyses were repeated using a multiplicative, allometric approach [29-31] to eliminate possible effects of body size, pulmonary function, and muscle function from the relationship between VO_2 peak and physical activity. This approach is based on the assumption that VO_2 peak is not linearly related to measures of body size, for example body mass M , but proportional to power functions of those measures, for example M to the power of an exponent x . Further covariates such as age can be incorporated in the multiplicative equation as additional factors (for example $VO_2\text{peak}=a\cdot M^x\cdot e^{y\cdot\text{age}}$). By log-transforming the model equation, an additive equation is generated ($\ln(VO_2\text{peak})=\ln(a)+x\cdot\ln(M)+y\cdot\text{age}$) which can be fitted to the data set by multiple linear regression analysis. There is both theoretical and experimental evidence supporting the use of this approach [30,31]. Briefly, additive linear regression models have been challenged for two reasons: 1) using an additive regression model with a positive intercept implies that, for example, a “hypothetical” individual with a

body weight of 0 kg may have a performance which is not zero. This “observation” would be in contrast to common sense. 2) Residuals over the additive predictor – performance regression model increase with increasing values of the predictor. In other words, the error over the regression is not additive but multiplicative. This observation is in contrast to the conditions for regression analysis.

For the allometric multiple regression analyses, the natural logarithm of VO_{2peak} was computed for each individual and entered as dependent variable in multiple linear regression analyses. We performed two separate analyses, one with average accelerometer count per day or time spent in MVPA allowed to enter the model and one with time spent in MVPA (model 2). For both analyses, the following additional variables were allowed to enter the prediction equations as independent predictors of $\ln(VO_{2peak})$: nationality (German or Swiss, to account for possible differences in laboratory and experimental configuration), gender, age, age^2 , $age \cdot gender$, $\ln(\text{height})$, $\ln(\text{body mass})$, %body fat, FVC (%predicted), FEV_1 (%predicted), $\ln(\text{TMW})$, SpO_2 at peak exercise, change in SpO_2 from rest to exercise, and Pseudomonas status.

After all significant predictors had entered model 1 or 2, average daily accelerometer count or time spent in MVPA were excluded from the respective model and the change in explained variance of $\ln(VO_{2peak})$ was calculated.

Significance was accepted at $p < 0.05$. Statistical analysis was performed using BMDP statistical software (BMDP Statistical Software Version 7.0, Cork, Ireland).

RESULTS

VO_{2peak} expressed relative to body weight and as a percentage of predicted was significantly related to the average daily accelerometer count and MVPA (Figure 1).

In model 1, the multiple regression analysis including average accelerometer count per day as measure of physical activity, five independent predictors of $\ln(VO_{2peak})$ entered the model in

the following order: ln(TMW), FEV1, average accelerometer count per day, ln(height), and gender. Once these predictors had entered the equation, none of the other variables could significantly add to the prediction of ln(VO₂peak).

Using time spent in MVPA as the activity variable allowed to enter the equation, the same additional predictors were identified as in model 1. However, time spent in MVPA entered the equation already at the second step of the analysis after ln(TMW) and before FEV1, ln(height), and gender were included.

Table 2 summarizes the regression coefficients of both models as determined from the multiple regression analyses. The coefficients reported in table 2 are exponents relating VO₂peak to FEV1, TMW, height and gender. In other words, VO₂peak in model 1 was proportional to $height^{1.5602}$, $TMW^{0.3556}$, $e^{0.00541 \cdot FEV1}$, $e^{-0.0999 \cdot gender}$, and $e^{0.000000429 \cdot \text{average accelerometer count per day}}$ in our group of patients with CF. In model 2, VO₂peak was proportional to $height^{1.5826}$, $TMW^{0.3612}$, $e^{0.00494 \cdot FEV1}$, $e^{-0.0895 \cdot gender}$, and $e^{0.00172 \cdot \text{time spent in MVPA}}$.

Removing average accelerometer count per day as predictor of ln(VO₂peak) in model 1 reduced the explained variance of ln(VO₂peak) by 2.5% from 78.5% to 76.0%. The explained variance of ln(VO₂peak) was reduced by 3.7% when time spent in MVPA was removed from model 2.

DISCUSSION

The current study shows that physical activity and aerobic capacity are related in patients with cystic fibrosis. At first, this finding does not seem surprising. However, only one study has previously assessed this relationship [9] and could not detect a significant correlation in a group of 30 patients with cystic fibrosis. In this latter study [9], only in the 10 patients with reduced pulmonary functions (FEV₁<80%), were physical activity and VO₂peak related. It is possible that the larger sample size in our study which also included adult subjects, the more advanced pulmonary disease of our subjects, and the more objective

method to measure physical activity (accelerometry vs. activity questionnaire) allowed us to detect the relationship. For the first time, we were able to show that VO_{2peak} was related to physical activity when the effects of body size, gender, lung function, and muscle power were taken into account. Most of these factors are related to both, physical activity and VO_{2peak} , and, thus, could have explained the relationship between them. Since the analysis revealed a significant relationship between physical activity and VO_{2peak} when the above factors were accounted for, an effect of physical activity on VO_{2peak} is shown that is not mediated by gender, lung function or muscle mass and function.

Several studies have shown that enhancement of physical activity may improve VO_{2peak} in patients with cystic fibrosis [5,17,32]. It is thus very likely that a high level of physical activity is beneficial for a high VO_{2peak} . It can, however, not be excluded that VO_{2peak} also influences physical activity. Associations of VO_{2peak} and quality of life measures such as physical functioning and body image have been reported [33] which might translate into positive attitudes towards physical activities in those patients who have a relatively high VO_{2peak} .

Multiple linear regression analysis using a multiplicative model identified body height, gender, FEV_1 , and muscle power – in addition to physical activity – as independent, significant predictors of VO_{2peak} . This finding is in line with the results of several studies in patients with CF showing that aerobic performance defined as VO_{2peak} is correlated with measures of lung function [11,13-15] and muscle power [16]. In healthy people, VO_{2peak} is related to age, gender, height, weight, and body composition [34,35].

Only one study has evaluated the effects of several independent predictors on VO_{2peak} in cystic fibrosis, employing a multiple linear regression analysis [16]. In that study, lean body mass, FEV_1 , and 30-s sprint work were allowed to enter the regression equation. Although lean body mass was significantly correlated with VO_{2peak} in a simple linear

regression analysis, the best model included only FEV₁ and the work generated during the 30-s sprint. Our results are in line with these findings but extend the number of significant independent predictors of VO₂peak beyond those described by Lands et al. [16] by also including physical activity, gender and height. Again, both latter variables are well known to correlate with aerobic capacity in healthy individuals [34,35].

There are several possible factors not included in the measurements of the present study which might explain the relationship between physical activity and VO₂peak even after the adjustment for body size, gender, lung function, and muscle power. For example, cardiovascular function and enzyme activities involved in oxidative metabolism were not directly measured in the current study. There may well be an effect of endurance type physical activities on these parameters which translates into an increase in VO₂peak. Furthermore, the effect of physical activities on VO₂peak may be mediated via a strengthening of respiratory muscles. In patients with chronic obstructive pulmonary disease, an exercise rehabilitation program resulted in an increase in inspiratory muscle force and VO₂peak but no improvements in FEV₁ [36].

In conclusion, physical activity is a significant – although relatively weak – predictor of VO₂peak in CF even when the effects of body size, gender, lung function, and short-term muscle power are taken into account. An increase in physical activity might, therefore, translate into an increase in VO₂peak independent of improvements in muscle power and lung function.

ACKNOWLEDGEMENTS

This study was supported by grants from the Mukoviszidose e.V. and the Swiss CF foundation.

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Table 1) Subjects' characteristics

	Number/Mean±SD	Range
Male / Female	35 / 36	---
Swiss / German	34 / 37	---
<i>P. aeruginosa</i> positive	52	---
Age (years)	20.5±6.0	12.2 – 40.0
Height (cm)	166±9	139 – 187
Body mass (kg)	53.8±10.8	30.0 – 86.0
Body fat (%)	15.9±7.2	2.9 – 30.4
FVC (%predicted)	79.8±17.8	37.0 – 117.9
FEV ₁ (%predicted)	66.0±21.1	25.3 – 107.4
MVPA (min/day)	85.1±36.1	10.0 – 175.9
VO ₂ peak (ml/min)	2004±549	761 – 3333
VO ₂ peak (ml/(min·kg))	37.5±8.1	19.3 – 55.0
VO ₂ peak (%predicted)	79.4±17.2	37.2 – 120.2
SpO ₂ peak (%)	92.8±4.9	92-100
ΔSpO ₂ (%)	-4.0±3.5	-13 – 1
RER (peak exercise)	1.08±0.11	0.83-1.30
HRpeak (min ⁻¹)	180±11	153-200
TMW (J)	10379±3335	5040-19904

Definition of abbreviations: FVC – forced vital capacity; FEV₁ – forced expiratory volume in 1 second; MVPA - moderate and vigorous physical activity; VO₂peak – peak oxygen uptake, SpO₂peak – oxygen saturation at peak exercise; ΔSpO₂ – change in oxygen saturation from

rest to peak exercise; RER – respiratory exchange ratio; HR_{peak} – highest heart rate during the incremental cycling task; TMW - total mechanical work during the Wingate test

Table 2) Significant independent predictors of $\ln(\text{VO}_2\text{peak})$ in patients with CF. The multiple linear regression models describe the data well.

	Model 1 ($r=0.89$, $r^2=0.79$)	Model 2 ($r=0.89$, $r^2=0.80$)
Predictor	Regression Coefficients	Regression Coefficients
Constant	-2.8050	-2.9520
FEV ₁ (%predicted)	0.00541±0.000978***	0.00494±0.00098***
Ln(TMW) (ln(J))	0.3556±0.10***	0.3612±0.09***
Ln(height) (ln(m))	1.5602±0.49**	1.5826±0.48**
Gender (male=1, female=2)	-0.0999±0.04*	-0.0895±0.04*
Measure of physical activity	Total accelerometer count per day 4.29·10 ⁻⁷ ±1.53·10 ⁻⁷ **	Daily time spent in moderate and vigorous activities (min) 0.00172±0.0005***

Regression coefficients are provided ±SE. * - $p<0.05$, ** - $p<0.01$, *** - $p<0.001$

FIGURE LEGENDS

Figure 1) Relationship between physical activity (**A,C**: total daily accelerometer count; **B,D**: time spent in moderate to vigorous activities (MVPA) per day) and VO_{2peak} expressed relative to body weight (**A,B**) and as a percentage of predicted (**C,D**) in 71 patients with cystic fibrosis. The relationship between physical activity and VO_{2peak} is significant irrespective of the way either variable is expressed.

