Eur Respir J 1997; 10: 2014–2017
DOI: 10.1183/09031936.97.10092014
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European Respiratory Journal
ISSN 0903 - 1936

Maximal work capacity in relation to nutritional status in children with cystic fibrosis

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ABSTRACT: In children with cystic fibrosis, objective parameters of exercise tolerance are needed which are easy to measure in nonspecialized centres. We investigated maximal workload (W'_{max}) in children with cystic fibrosis in relation to body weight and fat-free mass, and compared this with results for maximal oxygen consumption ($V'_{O_2,max}$).

Fourteen patients with cystic fibrosis performed an incremental maximal exercise test on a bicycle ergometer. W'_{max}, $V'_{O_2,max}$, body weight and fat-free mass were measured.

W'_{max} and $V'_{O_2,max}$ were significantly correlated (r=0.91; p<0.001). Using standard deviation scores in relation to reference values, W'_{max} and $V'_{O_2,max}$ per kilogram body weight were significantly higher than uncorrected W'_{max} and $V'_{O_2,max}$ (mean difference (95% CI) 0.63 (0.24–1.01) and 0.91 (0.32–1.49) SD units, respectively). There was no such difference after correction for fat-free mass. Standardized $V'_{O_2,max}$ was significantly higher than standardized W'_{max} (mean difference (95% CI): 1.59 (1.14–2.04)), also after correction for body weight and fat-free mass.

In children with mild-to-moderate cystic fibrosis, maximal workload per kilogram fat-free mass, but not per kilogram body weight, is a useful parameter to correct for diminished nutritional status. In these patients, maximal workload is consistently lower than maximal oxygen consumption. Taking into account this difference, maximal workload and maximal workload per kilogram fat-free mass can be used for follow-up of paediatric patients with cystic fibrosis in nonspecialized settings.
Eur Respir J 1997; 10: 2014–2017.

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Keywords: Children
cystic fibrosis
exercise
nutritional status

Received: November 7 1996
Accepted after revision May 9 1997

Presented at the annual congress of the European Respiratory Society, 1995, Barcelona, Spain.

In patients with cystic fibrosis (CF), deterioration of lung function and nutritional status is often seen, and clinical deterioration in these patients is associated with decreased exercise tolerance. Nutritional status and exercise tolerance in CF patients are associated with prognosis and survival [1, 2], and their preservation is thus important [3]. Exercise programmes have been shown to improve exercise tolerance in children and adults with CF [4–12]. For monitoring of exercise programmes in individual patients, easy and reliable measurements of exercise capacity with correction for nutritional status are needed. However, adequate methods to this purpose are not readily available.

Routine measurement of maximal exercise tolerance is performed with bicycle ergometry or treadmill tests under standardized conditions [13–15]. Major parameters of exercise tolerance are maximal oxygen consumption ($V'_{O_2,max}$), endurance time or covered walking distance in treadmill tests, and maximal workload (W'_{max}) in bicycle ergometer tests [13]. Reference values are available for these parameters in normal adults [13–15] and children [16, 17]. However, in children, body height, body weight (BW) and, in particular, fat-free mass (FFM) are associated with exercise parameters and with age. Exercise performance tests in CF are generally thought to give information on the patient's cardiopulmonary fitness, but this cannot be done unless exercise parameters are corrected for the patient's nutritional status [18]. Thus, apart from age, correction for nutritional status parameters is needed before conclusions on exercise parameters can be made [19]. MARCOTTE *et al.* [20] showed that, in CF patients, nutritional status plays a significant role in determining exercise capacity. From these observations, it follows that absolute values of exercise performance in CF patients should be compared with reference values for healthy children with correction for nutritional status. Reference values for $V'_{O_2,max}$ expressed per kilogram body weight ($V'_{O_2,max} \cdot kg^{-1}$) and W'_{max} corrected for BW and FFM in children are available [16, 17, 19]. However, measurement of $V'_{O_2,max}$ requires sophisticated equipment, which is often unavailable outside specialized centres, whereas maximal work capacity can be measured in any setting when a bicycle ergometer is available.

The aim of the present study was to investigate whether W'_{max} as compared to $V'_{O_2,max}$ can be used to assess exercise capacity in children with CF performing an incremental maximal exercise test, and which correction for nutritional status is useful.

Subjects and methods

Subjects

We studied 14 children with cystic fibrosis (mean age (SD) 14.8 (1.7) yrs, eight boys and six girls), who regularly attended the out-patient clinic of our hospital and were able to perform an exercise test. Other inclusion criteria were: a stable clinical condition; and a forced expiratory volume in one second (FEV_1) <90% of predicted value [21]. None of the patients showed clinical signs of asthma or atopy. All patients participated in gymnastics at school, three were also active in sports. None of the patients needed a daily oxygen supply. The patients' characteristics are presented in table 1.

Methods

An incremental maximal exercise test was performed on an electronically braked bicycle ergometer (Lode Examiner; Lode, Groningen, The Netherlands; accuracy 1%), at least 1 h after a light lunch. In order to reach the subject's maximum in 8–15 min, stepwise increments of 10 or 15 $W \cdot min^{-1}$ were chosen; the 10 W protocol was used in patients with FEV_1 <70% and/or body height <1.70 m, and the 15 W protocol in the remaining patients. W'_{max} was defined as the highest workload maintained during the last 30 s of sustained workload. All tests were conducted by the same researcher (VAMG). The patients were encouraged to perform to the best of their abilities throughout the test.

Continuous breath by breath respiratory gas analysis and volume measurements were performed and automatically stored in a machine (Oxycon Champion; Jaeger, Breda, The Netherlands), using a Triple V valveless mouthpiece, while the nose was blocked with a clip. Oxygen and carbon dioxide concentrations were measured with a paramagnetic O_2 analyser (Datex, Helsinki; accuracy 0.02% O_2) and an infra-red CO_2 analyser (Datex, Helsinki; accuracy 0.01% CO_2), respectively. Internal gas and volume calibration was performed before each measurement according to the instructions of the manufacturer, as described by ZOLADZ and co-workers [23]. Oxygen consumption was computed automatically and gas volumes were expressed under standard conditions (0°C and 100 kPa). Cardiac frequency (of 3-leads electrocardiograph (ECG); Hewlett-Packard, Amsbelveen, The Netherlands) and transcutaneous oxygen saturation (pulse oximetry; Nelcorr 200 E; Breda, the Netherlands) were also monitored continuously. At rest and 3 min after reaching W'_{max}, capillary blood samples were taken from the middle finger. The heparinized samples were placed on ice for determination of the plasma lactate concentration (enzymatic method, ACA® discrete clinical analyser; Du Pont de Nemours, Nemours, France). Efforts were considered to be at a maximum level if at least two out of three criteria were met: 1) cardiac frequency above 180 $beats \cdot min^{-1}$; 2) maximal respiratory exchange ratio (*i.e.* ratio of carbon dioxide production over oxygen consumption (V'_{CO_2}/V'_{O_2})) above 1.0; and 3) increase in lactate concentration above threshold levels in age-matched controls as described by DAVIES *et al.* [16]. All patients fulfilled at least two criteria (table 2).

BW was measured with an electronic scale (ID1 multimap; Mettler, Tiel, The Netherlands; accuracy 20 g). FFM was calculated from the measurements of the four left-sided skinfolds (biceps, triceps, subscapular region and above the crista iliaca) with a Holtain calliper (Crymych, UK; accuracy 0.1 mm), according to the method described by DURNIN and RAHAMAN [24].

The study was approved by the Medical Ethics Committee and the Research Council of the University Hospital for Children and Youth "Wilhelmina Children's Hospital" and informed consent was obtained in all cases.

Table 1. – Characteristics of the patients studied

Variable	Mean	SD
Age yrs	14.8	1.7
FEV_1 % pred	59	16
FVC % pred	75	14
MEF_{50} % pred	35	18
RV/TLC %	46	7
Height cm	158.7	9.6
Height Z-score SD units	-0.7	1.0
Weight kg	42.7	9.2
Weight Z-score SD units	-1.4	0.6
Fat-free mass kg	35.8	8.3
S_{tc,O_2} at rest %	96	1
Shwachman-score (0–100)	71	11

Body weight and height for age were transformed into standard deviation scores (Z-scores, reference value from the National Center for Health Statistics, USA [22]). FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; MEF_{50}: maximum expiratory flow at 50% FVC; RV/TLC: residual volume to total lung capacity ratio; S_{tc,O_2}: transcutaneous oxygen saturation; % pred: percentage of predicted value.

Statistical analysis

Kolmogorov-Smirnov goodness-of-fit tests showed no significant deviations with respect to the assumption of normality of distribution for all variables. Correlation analyses (Pearson's r) were performed for W'_{max}, $V'_{O_2,max}$, BW and FFM. The ratios of W'_{max} and $V'_{O_2,max}$ both with BW and FFM were calculated. Standard deviation scores (Z-scores, expressed in SD units) were calculated for W'_{max}, W'_{max}/BW ratio, W'_{max}/FFM ratio and $V'_{O_2,max}$, $V'_{O_2,max}$/BW ratio, $V'_{O_2,max}$/FFM ratio from reference values obtained in healthy Dutch children [19, 25]. Individual values were also compared to the 3rd percentile (P_3) of the reference population (the P_3 corresponds with a Z-score of -1.88). Mean differences between Z-scores and 95% confidence intervals (95% CI) were calculated from paired t-tests. The Statistical Package for the Social Sciences (SPSS) PC^+ package (version 5.0) was used for analysis [26]. A p-value of less than 0.05 was considered significant.

Results

In all patients, exercise tests met the criteria for maximal performance. Exercise parameters are summarized in table 2. Results for W'_{max} and $V'_{O_2,max}$ and the Z-scores of these parameters in individual patients before and after correction for nutritional status are presented in table 3. BW and FFM were associated with W'_{max} (r=0.66; p<0.01) and (0.79; p<0.001), respectively and $V'_{O_2,max}$

Table 2. – Exercise parameters at peak exercise

Variables		
Workload W	122±42	(70–202)
V'_{O_2} mL	1732±482	(1204–2521)
f_C $beats \cdot min^{-1}$	173±12	(142–197)
Plasma lactate concentration $mmol \cdot L^{-1}$	7.4±2.7	(3.2–13.2)
Respiratory exchange ratio	1.16±0.08	(1.07–1.36)
S_{tc,O_2} %	93±2	(89–97)
V'_{O_2} per heart beat $mL \cdot beat^{-1}$	9.9±2.6	(7.0–14.2)

Values are presented as mean±SD, and range in parenthesis. V'_{O_2}: oxygen consumption; f_C: cardiac frequency; S_{tc,O_2}: transcutaneous oxygen saturation.

Table 3. – Absolute values of maximal workload and maximal oxygen consumption, and standard deviation scores (Z) with and without correction for nutritional status

Pt No.	W'_{max} W	$Z(W'_{max})$ SD unit	$Z(W'_{max}/BW)$ SD unit	$Z(W'_{max}/FFM)$ SD unit	$V'_{O_2,max}$ $mL \cdot min^{-1}$	$Z(V'_{O_2,max})$ SD unit	$Z(V'_{O_2,max}/BW)$ SD unit	$Z(V'_{O_2,max}/FFM)$ SD unit
1	202	-1.91	-0.86	-1.48	2521	-1.20	0.50	-0.07
2	70	-4.77	-4.83	-6.17	1216	-2.46	-2.32	-3.75
3	90	-2.84	-1.88	-2.68	1379	-1.74	-0.06	-0.85
4	150	-2.10	-1.94	-3.14	1857	-0.86	-0.70	-1.87
5	105	-2.70	-1.57	-2.17	1639	-0.65	1.54	1.23
6	188	-3.03	-3.76	-3.90	2497	-1.76	-2.46	-2.49
7	143	-2.93	-1.43	-1.60	1806	-2.24	0.22	0.12
8	165	-4.57	-2.91	-3.38	2069	-3.08	-1.90	-2.48
9	80	-3.63	-2.96	-3.31	1351	-1.37	-0.32	-0.51
10	100	-3.77	-3.87	-3.60	1714	-1.21	-1.70	-1.65
11	80	-3.63	-3.16	-3.31	1204	-1.49	-1.24	-0.86
12	100	-3.42	-2.58	-3.45	1303	-2.74	-2.08	-3.20
13	100	-4.32	-4.14	-4.64	1285	-3.54	-3.22	-3.64
14	135	-3.19	-2.16	-3.02	2416	-0.21	1.86	2.64
Mean	122	-3.34	-2.72	-3.28	1733	-1.75	-0.85	-1.24
SD	42	0.85	1.15	1.19	482	0.96	1.54	1.86
p-value*		<0.001	<0.001	<0.001		<0.001	0.08	0.05

W'_{max}: maximal workload; $Z(W'_{max})$: SD score of maximal workload; $Z(W'_{max}/BW)$: SD score of the ratio of maximal workload and body weight; $Z(W'_{max}/FFM)$: SD score of the ratio of maximal workload and fat-free mass; $V'_{O_2,max}$: maximal oxygen consumption; $Z(V'_{O_2,max})$: SD score of the ratio of maximal oxygen consumption; $Z(V'_{O_2,max}/FFM)$: SD score of the ratio of maximal oxygen consumption and fat-free mass. *: t-test, comparing mean Z-score of cystic fibrosis (CF) patients with median reference population (which corresponds with Z-score of 0).

($r=0.63$; $p<0.01$) and (0.74; $p<0.001$), respectively. Results for $V'_{O_2,max}$ and W'_{max} showed a high correlation within the patient group ($r=0.91$; $p<0.001$). However, W'_{max} was below the 3rd percentile in all patients, but only 5 out of 14 patients had a $V'_{O_2,max}$ $<P_3$. The mean Z-score for $V'_{O_2,max}$ was significantly higher than the Z-score for W'_{max} (mean difference 1.59; 95% CI 1.14–2.04 SD units).

Comparisons of the standardized exercise parameters showed significantly higher Z-scores for W'_{max}/BW ratio than for W'_{max} (mean difference 0.63; 95% CI 0.24–1.01 SD units), but not for W'_{max}/FFM ratio and W'_{max} (mean difference -0.07; 95% CI -0.52–0.38). Likewise, for $V'_{O_2,max}$, significantly higher Z-score values existed after correction for BW (mean difference between $Z(V'_{O_2,max}/BW)$ and $Z(V'_{O_2,max})$ 0.91; 95% CI 0.32–1.49), but standardized scores for $V'_{O_2,max}/FFM$ ratio and $V'_{O_2,max}$ were not significantly different (mean difference 0.51; 95% CI -0.22–1.24). Nine of the 14 patients had a $V'_{O_2,max}$/ BW $>P_3$, and three patients had a $V'_{O_2,max}$ exceeding the median of the reference population.

Discussion

In this study, we compared maximal workload measurements in children with CF and addressed the correction of W'_{max} and $V'_{O_2,max}$ for nutritional status. Our results showed that in the CF patients, Z-scores for W'_{max}/BW ratio reach significantly higher values than Z-scores for W'_{max} and W'_{max}/FFM ratio. This was also found for the respective parameters of $V'_{O_2,max}$. In normal children, there is a higher correlation between FFM and W'_{max} and $V'_{O_2,max}$ than between BW and these exercise parameters [19], as FFM is a better correlate for body muscle mass than BW. The clinically declined CF patients in this study also showed high correlations between W'_{max} (and $V'_{O_2,max}$) and FFM. Moreover, the Z-scores for these exercise parameters after correction for FFM were not significantly different from the uncorrected Z-scores, whereas Z-scores with correction for BW were significantly higher. This can be explained by the greater level of fat depletion in undernourished CF patients, resulting in a higher proportion of FFM per unit of BW, and by the fact that exercise capacity is mainly dependent on FFM. Thus, correction for BW seems to overestimate the work capacity in patients with CF. These results are in agreement with those in the study by LANDS *et al.* [18], in which differences in $V'_{O_2,max}$ between adult CF patients and controls persisted after correction for FFM. The results suggest that W'_{max} and $V'_{O_2,max}$ can both be used for the follow-up of children with CF.

Although the highly significant correlation between W'_{max} and $V'_{O_2,max}$ in the present study group ($r=0.91$; $p< 0.001$) is in agreement with results of previous studies in healthy subjects [13, 15, 27], we found a significant difference between standardized W'_{max} and $V'_{O_2,max}$ in the children with CF. In this group of patients with mild-to-moderate symptoms, $V'_{O_2,max}$ and even more the ratios $V'_{O_2,max}/BW$ and $V'_{O_2,max}/FFM$ had persistently higher Z-scores than their W'_{max} counterparts (table 3). Surprisingly, the patients had a relatively good level of $V'_{O_2,max}$ and $V'_{O_2,max}/BW$ (nine out of 14 patients were in the normal range). However, these children had a high degree of impairment with respect to W'_{max} ($<P_3$ in all patients). These results are different from those of LANDS *et al.* [18], who found no excessive $V'_{O_2,max}$ as compared to W'_{max} in a group of 14 adult patients with CF. Methodological factors in the measurement of W'_{max} and $V'_{O_2,max}$ are unlikely to explain the discrepancy between W'_{max} and $V'_{O_2,max}$ in the children in the present study.

Thus, biological explanations for the observed discrepancy in results for W'_{max} and $V'_{O_2,max}$ should be considered. Pulmonary function in these patients with CF was diminished, limiting their maximal oxygen uptake in the lungs. However, both before and after correction for BW, $V'_{O_2,max}$ in the CF patients was better preserved than W'_{max} output. If oxygen uptake in the lungs (or oxygen transport by the blood) was the limiting factor for maximal performance in this patient group, we cannot explain the latter finding. In children, muscle mass (and FFM and BW) is associated with W'_{max} and also with $V'_{O_2,max}$. The lower BW and FFM in the CF patients as compared to their peers in the reference population would affect both W'_{max} and $V'_{O_2,max}$, and thus differences in nutritional status do not seem to explain the observed discrepancies between the Z-scores for W'_{max} and $V'_{O_2,max}$. The higher standardized scores for $V'_{O_2,max}$ as compared to W'_{max} suggest that, relative to healthy peers in the Dutch reference population, the children with CF in the present study consumed more oxygen at a given level of workload. This hypothesis is supported by a previous study in children with CF, which showed a lower efficiency of adenosine triphosphate (ATP) synthesis during *in vivo* oxidative power generation in skeletal muscle as compared to controls [28]. However, even after correcting maximal workload for age, gender, and nutritional status, other clinical factors, such as drugs, bacterial colonization and genotype, may influence maximal work performance in children with CF, and thus no inferences can be made on the cause of the discrepancy between $V'_{O_2,max}$ and W'_{max} in this patient group. Further studies in patients with CF in different clinical conditions and in different age groups are needed to address the observation of diminished work performance in relation to oxygen consumption.

We conclude that, in children with mild-to-moderate cystic fibrosis, maximal work output can be used as a parameter for physical fitness. Correction for nutritional status should include the ratio of maximal workload and fat-free mass, which according to our results seems a useful parameter for that purpose. In the children with cystic fibrosis, strong associations existed between maximal workload and maximal oxygen consumption. As compared to healthy children, maximal workload in the patients with cystic fibrosis were lower than maximal oxygen consumption, after correction for nutritional status. When this is taken into account, maximal workload and the ratio of maximal workload and fat-free mass are an alternative to maximal oxygen consumption and the ratio of maximal oxygen consumption and fat-free mass for the assessment, and especially the follow-up, of exercise tolerance in clinically declined children and adolescents with cystic fibrosis. This is of particular importance for settings where equipment for gas analysis is not available.

***Acknowledgements*:** The authors thank J.A.J. Faber (Utrecht University, Centre for Biostatistics) for statistical comments, and Nutricia B.V. (Zoetermeer, The Netherlands) for financial support.

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