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

V.A.M. Gulmans*, K. de Meer**, H.J.L. Brackel†, P.J.M. Helders*


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'\text{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'\text{max}, V'O_2,max, body weight and fat-free mass were measured.

W'\text{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'\text{max} and V'O_2,max per kilogram body weight were significantly higher than uncorrected W'\text{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'\text{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.


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'\text{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·kg−1) and W'\text{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'\text{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

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were able to perform an exercise test. Other inclusion criteria were: a stable clinical condition; and a forced expiratory volume in one second (FEV1) <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·min⁻¹ were chosen; the 10 W protocol was used in patients with FEV1 <70% and/or body height <1.70 m, and the 15 W protocol in the remaining patients. Wmax 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 type mouthpiece, while the nose was blocked with a clip. Oxygen and carbon dioxide concentrations were measured with a paramagnetic O₂ analyser (Datex, Helsinki; accuracy 0.02% O₂) and an infra-red CO₂ analyser (Datex, Helsinki; accuracy 0.01% CO₂), respectively. Internal gas and volume calibration was performed before each measurement according to the instructions of the manufacturer, as described by ZOŁADZ 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, Amselven, The Netherlands) and transcutaneous oxygen saturation (pulse oximetry; Nelcor 200 E; Breda, the Netherlands) were also monitored continuously. At rest and 3 min after reaching Wmax, 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-min⁻¹; 2) maximal respiratory exchange ratio (i.e. ratio of carbon dioxide production over oxygen consumption (V’CO₂/V’O₂)) 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 multipum; Mettler, 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 ilia) 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.

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 Wmax, V’O₂,max, BW and FFm. The ratios of Wmax and V’O₂,max both with BW and FFm were calculated. Standard deviation scores (Z-scores, expressed in SD units) were calculated for Wmax, Wmax/BW ratio, Wmax/FFm ratio and V’O₂,max/BW ratio, V’O₂,max/FFm ratio from reference values obtained in healthy Dutch children [19, 25]. Individual values were also compared to the 3rd percentile (P₃) of the reference population (the P₃ 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 Wmax and V’O₂,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 Wmax (r=0.66; p<0.01) and (0.79; p<0.001), respectively and V’O₂,max

Table 1. – Characteristics of the patients studied

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>14.8</td>
<td>1.7</td>
</tr>
<tr>
<td>FEV1 % pred</td>
<td>59</td>
<td>16</td>
</tr>
<tr>
<td>FVC % pred</td>
<td>75</td>
<td>14</td>
</tr>
<tr>
<td>MEF50 % pred</td>
<td>35</td>
<td>18</td>
</tr>
<tr>
<td>RV/TLC %</td>
<td>46</td>
<td>7</td>
</tr>
<tr>
<td>Height cm</td>
<td>158.7</td>
<td>9.6</td>
</tr>
<tr>
<td>Height Z-score SD units</td>
<td>-0.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Weight kg</td>
<td>42.7</td>
<td>9.2</td>
</tr>
<tr>
<td>Height Z-score SD units</td>
<td>-1.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Fat-free mass kg</td>
<td>35.8</td>
<td>8.3</td>
</tr>
<tr>
<td>Sct,O₂ at rest %</td>
<td>96</td>
<td>1</td>
</tr>
<tr>
<td>Shwachman-score (0–100)</td>
<td>71</td>
<td>11</td>
</tr>
</tbody>
</table>

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]). FEV1: forced expiratory volume in one second; FVC: forced vital capacity; MEF50: maximum expiratory flow at 50% FVC; RV/TLC: residual volume to total lung capacity ratio; Sct,O₂: transcutaneous oxygen saturation; % pred: percentage of predicted value.

Table 2. – Exercise parameters at peak exercise

<table>
<thead>
<tr>
<th>Variables</th>
<th>Workload W</th>
<th>V’O₂, mL</th>
<th>f/c beats-min⁻¹</th>
<th>Plasma lactate concentration mmol·L⁻¹</th>
<th>Respiratory exchange ratio</th>
<th>Sct,O₂ %</th>
<th>V’O₂ per heart beat mL·beat⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>122±42</td>
<td>1732±482</td>
<td>173±12</td>
<td>7.4±2.7</td>
<td>1.16±0.08</td>
<td>93±2</td>
<td>9.9±2.6</td>
</tr>
</tbody>
</table>

Values are presented as mean±sd, and range in parenthesis. V’O₂: oxygen consumption; f/c: cardiac frequency; Sct,O₂: transcutaneous oxygen saturation.
and undernourished children, there is a higher correlation between FFM and body weight; Z(Wmax) and Z(Wmax/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'O2,max between adult CF patients and controls persisted after correction for FFM. The results suggest that Wmax and V'O2,max can both be used for the follow-up of children with CF.

Although the highly significant correlation between Wmax and V'O2,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 Wmax and V'O2,max in the children with CF. In all patients, including those with mild-to-moderate symptoms, V'O2,max and even more the ratios V'O2,max/BW and V'O2,max/FFM had persistently higher Z-scores than their Wmax counterparts (table 3). Surprisingly, the patients had a relatively good level of V'O2,max and V'O2,max/BW (nine out of 14 patients were in the normal range). However, these children had a high degree of impairment with respect to Wmax (<P3 in all patients). These results are different from those of LANDS et al. [18], who found no excessive V'O2,max as compared to Wmax in a group of 14 adult patients with CF. Methodological factors in the measurement of Wmax and V'O2,max are unlikely to explain the discrepancy between Wmax and V'O2,max in the children in the present study.

Thus, biological explanations for the observed discrepancy in results for Wmax and V'O2,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'O2,max in the CF patients was better preserved than Wmax 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 body weight; Z(Wmax) and Z(Wmax/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'O2,max between adult CF patients and controls persisted after correction for FFM. The results suggest that Wmax and V'O2,max can both be used for the follow-up of children with CF.

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(and FFM and BW) is associated with $W^{\text{max}}$ and also with $V'O_{2}^{\text{max}}$. The lower BW and FFM in the CF patients as compared to their peers in the reference population would affect both $W^{\text{max}}$ and $V'O_{2}^{\text{max}}$, and thus differences in nutritional status do not seem to explain the observed discrepancies between the Z-scores for $W^{\text{max}}$ and $V'O_{2}^{\text{max}}$. The higher standardized scores for $V'O_{2}^{\text{max}}$ as compared to $W^{\text{max}}$ 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 $V'O_{2}^{\text{max}}$ and $W^{\text{max}}$ 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.

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References