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Estimating peak oxygen uptake in adolescents with cystic fibrosis

Maarten S Werkman,1 Erik H J Hulzebos,1 Paul J M Helders,1 Bert G M Arets,2 Tim Takken1,3

ABSTRACT

Objectives To predict peak oxygen uptake (VO2peak) from the peak work rate (Wpeak) obtained during a cycle ergometry test using the Godfrey protocol in adolescents with cystic fibrosis (CF), and assess the accuracy of the model for prognostication clustering.

Methods Out of our database of anthropometric, spirometric and maximal exercise data from adolescents with CF (N=363; 140 girls and 223 boys; age 14.77 ±1.73 years; mean expiratory volume in 1 s (FEV1%pred) 86.82±17.77%), a regression equation was developed to predict VO2peak (mL/min). Afterwards, this prediction model was validated with cardiopulmonary exercise data from another 60 adolescents with CF (28 girls, 32 boys; mean age 14.6±1.67 years; mean FEV1%pred 85.43 ±20.01%).

Results We developed a regression model VO2peak (mL/min)=216.53–138.7×sex (0=male; 1=female) +11.5×Wpeak, R2=0.91; SE of the estimate (SEE) 172.57. A statistically significant difference (107 mL/min; p<0.001) was found between predicted VO2peak and measured VO2peak in the validation group. However, this difference was not clinically relevant because the difference was within the SEE of the model. Furthermore, we found high positive predictive and negative predictive values for the model for prognostication clustering (PPV 87% vs NPV 82–94%).

Conclusions In the absence of direct VO2peak assessment it is possible to estimate VO2peak in adolescents with CF using only a cycle ergometer. Furthermore, the regression model showed to be able to discriminate patients in different prognosis clusters based on exercise capacity.

INTRODUCTION

Cystic fibrosis (CF) is the most common lethal autosomal recessive childhood disorder in the white population, occurring in approximately 1 in 2500 births. The disease is caused by a defect of the CF transmembrane conductance regulator gene, which causes clinical manifestations in multiple organ systems, such as the lungs, intestines and pancreas.1 Low exercise capacity has been reported in children and adolescents with CF which seems to have a multifactorial cause.2 Furthermore, significant associations have been reported between exercise capacity of patients with CF and survival over an 8–10-year period.3 4 The most important parameter of aerobic exercise capacity is peak oxygen uptake (VO2peak),5–8 commonly defined as the highest oxygen uptake attained during a single progressive cardiopulmonary exercise test (CPET).9 CPET plays an important role in CF care and follow-up because of its contributing diagnostic, prognostic and functional information.10

As mentioned previously, VO2peak is a significant predictor of subsequent mortality, both as percentage of predicted3 10 or as absolute value of mL min/kg.4 Pianosi states that a VO2peak<32 mL min/kg was associated with a 10-year mortality of 50%, whereas a VO2peak>45 mL min/kg showed an association of 100% in a 10-year survival.4 Despite its clinical and prognostic value, many specialised CF centres still do not perform exercise testing, with or without gas analysis. A recent survey in UK CF clinics indicated that availability of resources to directly measure VO2peak (metabolic gas analysis system with treadmill or cycle ergometer) was the main reason for this.11 In centres without CPET possibilities, walking tests are frequently used as an alternative for VO2peak assessments because they offer a simple and inexpensive means of estimating exercise capacity.11 12 Recent evidence however suggests that these field tests are not very strongly associated with VO2peak in children and adolescents with CF.13

The Godfrey protocol14 is a validated cycle protocol to measure VO2peak and has been designed to induce exhaustion within 10–12 min, and is frequently used in patients with CF.15 16 Using an incremental exercise test protocol, a strong relation...
between VO2peak and Wpeak has been reported (coefficients of
determination (R^2) 0.98±0.03) in healthy children^17 and in ado-
lescents with CF (r=0.91; p<0.001).^18

This might implicate that, theoretically, CPET using the
Godfrey protocol measuring only Wpeak (ie, without gas ana-
lysis) could provide an alternative and valid method for the pre-
diction of VO2peak in adolescents with CF. A valid and
inexpensive exercise test may help to increase the use of exercise
testing in the clinical care and research of this patient
group.^11 12 19 20 Furthermore, more thorough assessment of
exercise capacity might have its impact on planning of lung
transplantation as exercise testing is considered as an important
prognostic tool for the selection of paediatric lung-transplant
candidates with end-stage CF.12

Therefore, in order to optimise the use of clinical exercise
testing, the objectives of this study were (1) to predict VO2peak
without gas analyses from Wpeak on a cycle ergometer, using the
Godfrey protocol in adolescents with CF and (2) assess the
accuracy of this prediction model for prognostication clus-
tering.

**MATERIAL AND METHODS**

**Study subjects**

Out of a database of anthropometric, spirometric and maximal
exercise data from adolescents with CF (=reference group;
N=363) tested in our laboratory between 1996 and 2006, a
regression equation was developed to predict VO2peak
(mL/min). Another 60 adolescents with CF (=validation group) also per-
formed a CPET using the Godfrey protocol at their annual
medical check-up. This group was used to validate the regres-
sion equation and to assess the accuracy of the model for pro-
gnostication clustering. Since exercise testing is a part of standard
medical care in our CF centre, no medical-ethical approval or
written informed consent was required according to the Dutch
law for medical research. The medical ethical committee of
the University Medical Centre Utrecht approved the use of the data-
base with anonymous patient care data of patients with CF for
scientific purposes.

Individual data were collected over the course of one visit.
Adolescents were asked to avoid heavy meals and strenuous
exercise as of the evening before their testing session. First, lung
function (Master Lab system, E Jaeger, Würzburg, Germany)
and anthropometric values, including weight and height were
measured using an electronic scale (Seca, Birmingham, UK) and
a stadiometer (Ulmer stadiometer, Professor E Heinze, Ulm,
Germany), respectively. This was followed by the performance
of the CPET. We used the anthropometric, spirometric and exer-
cise data of the patients in the database who performed a
maximal effort (HRpeak>180 bpm,^21 RERpeak>1.0 and subject-
ive signs of voluntary exhaustion. For a maximal effort, partici-
pants had to meet all the criteria.^9

**Godfrey exercise protocol**

The Godfrey protocol was performed on an electronically
braked cycle ergometer (Lode Corrival, Procure BV, Groningen,
The Netherlands). Participants began with unloaded cycling and
the workload increased every minute in a fixed interval based
on height (10 W/min<120 cm; 15 W/min 120–150 cm; 20 W/
min≥150 cm), independent of sex, until the patient stopped
due to volitional exhaustion.14 Throughout the test, adolescents
breathed into a mouthpiece connected to a calibrated metabolic
cart (ZAN 600, Accuramed Bv, Lumen, Belgium). Expired gas
passed through a flow metre, oxygen analyser, and a carbon
dioxide analyser. The flow metre and gas analyser were con-
ected to a computer, which calculated breath-by-breath minute
ventilation (VE), oxygen uptake (VO2), carbon dioxide produc-
tion (VCO2), and respiratory exchange ratio (RER) from con-
ventional equations. Heart rate (HR) was also monitored
continuously by a 12-lead electrocardiogram (Cardioperfect,
Accuramed Bv, Lumen, Belgium), and transcutaneous oxygen
saturation (SpO2%) was measured by a pulse oximeter placed
on the index finger (Nellcor 565, Coviedien, Zaltbommel, The
Netherlands). Peak exercise parameters were defined as the
mean values achieved during the final 30 s of the test.

**Statistical analysis**

Data were expressed as mean±SD. Data were analysed using
SPSS PASW Statistics V17.0 for Windows (SPSS, Chicago,
Illinois, USA) and tested for normality with the Kolmogorov–
Smirnov Test. A p value of <0.05 was considered statistically
significant. A linear regression model (backwards-elimination
procedure) from the data of the reference group was used to
predict VO2peak (mL/min) based on the Wpeak combined with
standard anthropometric variables based on biological plausibil-
ity (height (cm), age (years), sex (0=male; 1=female) and lung
function (FEV1 (L/min)). Variables were excluded from the
regression when p>0.1. Exercise data of the validation group
were used to measure the accuracy of the model for prognosti-
cation clustering. Paired sample t tests or Wilcoxon signed ranks
tests were used to analyse possible differences between actual
and predicted VO2peak. A Bland–Altman plot was used to assess
any systematic bias between measured VO2peak and predicted
VO2peak. Additionally, the same linear regression procedure as
for the reference group was performed in the validation group
to analyse for different variables being entered in the model.

Thereafter, the measured and predicted VO2peak of the partici-
pants in the validation group who performed a maximal effort
were clustered in three prognostic groups based on high
(>45 mL min/kg), medium (32–45 mL min/kg) and low (<32 mL/
min/kg) VO2peak, as previously described by Pianosi et al.^4

**RESULTS**

Out of a database of anthropometric, spirometric and maximal
exercise, data from adolescents with CF (=reference group)
(N=363, 140 girls and 223 boys, mean age 14.77±1.73 years,
and mean FEV1pred 86.82±17.77%) were tested in our labora-
tory between 1996 and 2006. The characteristics of the refer-
ence group are presented in table 1.

**Prediction of the VO2peak from the Wpeak**

Linear regression revealed the following equation (95% predic-
tion interval between 1770 and 2548 mL/min), with Wpeak and
sex as the only significant contributors (see table 2).

$$VO2\text{peak (mL/min)} = 216.3 - 138.7 \times \text{Sex}(0 = \text{female} / 1 = \text{male}) + 11.5 \times W\text{peak}$$

The greatest contributor to this regression equation was Wpeak followed by sex. When all the variables were entered in the
equation, age (β=−0.02; p=0.42), height (β=−0.02; p=0.41) and FEV1 (β=0.03; p=0.34) did not make a significant
additional contribution.

**Cross-validation**

All 60 participants in the validation group successfully per-
formed CPET without complications or adverse events. Descriptive characteristics are presented in table 1.
Based on previous mentioned criteria, 36 performed a maximal effort (20 female and 16 male, age 14.6±1.7 years, FEV1 86.89±18.67%, HRpeak 188±7 bpm, RERpeak 1.16 ±0.08). Their data were used to calculate the differences between measured and predicted VO2peak.

We found a small but statistically significant difference (mean difference 107 mL/min; p<0.01) between predicted VO2peak (2231±530 mL/min) and measured VO2peak (2125±544 mL/min). However, Bland–Altman analysis and an XY plot showed no systemic bias, with acceptable limits of agreement (see figures 1 and 2).

Furthermore, linear regression revealed the following equation for the validation group, with Wpeak (standardised β=0.83; p<0.001) and sex (standardised β=−0.17; p=0.038) as the only significant contributors:

\[
\text{VO2peak (mL/min)} = 377.0 - 178.4 \times \text{Sex (0=female/1=male)} + 10.1 \times W\text{peak} \quad R = 0.921; \quad R^2 = 0.848; \quad \text{SEE}=218.48; \quad p<0.001
\]

**Prognostics**

The positive predictive values for the model to correctly assign patients to the low, medium or high VO2peak prognosis group were 87%, 74% and 50%, respectively. The negative predictive value for the model to correctly assign patients as not having a low, medium or high VO2peak were 86%, 82% and 94%, respectively (see table 3).

**DISCUSSION**

The objectives of this study were (1) to predict VO2peak from Wpeak on a cycle ergometer using the Godfrey protocol in adolescents with CF and (2) assess the accuracy of the model for prognostication clustering.

We found a strong (R^2=0.91; SE of the estimate (SEE) =172.57) prediction model to predict VO2peak (mL/min) out of Wpeak and sex in a group of adolescents with CF with a large range in pulmonary function (FEV1 (147%)) with a 95% prediction interval between 1770 till 2548 mL/min. This result is in line with a previous study, which reported a strong relation between VO2peak and Wpeak (coefficients of determination (R^2) 0.98±0.03) in healthy children and in children with CF (r=0.91; p<0.001). However, the slope of the VO2 as response to the work-rate increment (ΔO2/ΔW) was higher in children with CF compared with healthy controls. This could suggest a high oxygen consumption of the respiratory muscles by a higher work of breathing in patients with lung disease.

In patients with CF, especially in a more severe disease status, several mechanisms become involved, such as an increased work of breathing during exercise.

Although we observed statistically significant differences between the predicted VO2peak and the measured VO2peak in the validation group (p<0.01), this difference (107 mL/min) was quite small and within the SEE of the model. Furthermore, the difference in VO2peak was smaller than the SE of measurement (SEM 138 mL/min (8.5%)) in a test-retest reliability study of VO2peak in adult patients with CF in a severe disease status (mean FEV1 52% of predicted, age 26.9±6.0). Linear regression analysis in the validation group with VO2peak as the dependent determinant revealed the same parameters as independent determinants with a comparable R^2 of 0.85 versus 0.91 in the reference group.

The results of this study have implications for clinical practice in adolescents with CF. When gas analysis is not available, Wpeak from the Godfrey protocol and sex may serve as clinical valid predictors of VO2peak in adolescents with CF in various disease states. The implementation of the Godfrey protocol and this equation in clinical practice might help to increase the use of exercise testing and measuring physical fitness in this patient group.

**Table 1** Patient characteristics and peak exercise data

<table>
<thead>
<tr>
<th>Reference group (n=363)</th>
<th>Validation group (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>14.77±1.73 [12.08–18.33]</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>51.31±11.39 [30.10–94.60]</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.20±10.75 [134.80–190.10]</td>
</tr>
<tr>
<td>Sex</td>
<td>223 females 140 males</td>
</tr>
<tr>
<td>FEV1% predicted (FEV1 (L))</td>
<td>86.82±17.77 (2.72±0.82)</td>
</tr>
<tr>
<td>HRpeak (bpm)</td>
<td>190±7 [180–210]</td>
</tr>
<tr>
<td>RERpeak</td>
<td>1.16 ±0.08</td>
</tr>
<tr>
<td>Wpeak (watt)</td>
<td>174±45 [75–300]</td>
</tr>
<tr>
<td>VO2peak (mL/min)</td>
<td>2151±571 [1000–3800]</td>
</tr>
</tbody>
</table>

HR, heart rate; RER, respiratory exchange ratio.

**Table 2** Final regression model

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Predictor variable</th>
<th>Unstandardised β</th>
<th>Standardised β</th>
<th>95% CI</th>
<th>p Value</th>
<th>95% PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2peak (mL/min)</td>
<td>Constant</td>
<td>216.342</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>−138.713</td>
<td>−0.118</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wpeak</td>
<td>11.445</td>
<td>0.897</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SEE, SE of the estimate.
We found high positive predictive values and high negative predictive values for the model to assign individual patients to different prognosis clusters. Only the positive predictive value for a low aerobic capacity (VO2peak < 32 mL min/kg) was low (50%), which can be explained by the low prevalence of a low aerobic capacity in the validation group (n=1). As Pianosi et al. found a VO2peak < 32 mL min/kg to be associated with a 10-year mortality of 50%, and a VO2peak > 45 mL min/kg to be associated with a 10-year mortality of 0%, the mean difference in VO2peak of our model (107 mL/min) is also quite accurate in a prognostic point of view. In our validation group with a mean weight of 50.44 kg, the difference in VO2peak between ‘good’ and ‘bad’ prognostic groups would be 635.7 mL/min (45 mL min/kg–32 mL min/kg), whereas the SEE of the model is 107 mL/min. Furthermore, the model is designed in a group of patients of varying prognosis (95% prediction interval between ∼23 mL min/kg and 2548 mL/min (∼50 mL min/kg). Additionally, calculated with the mean weight of the validation group, the predicted group means VO2peak and estimated VO2peak were both within the same prognosis cluster of Pianosi et al. (predicted VO2peak 44.23 mL min/kg vs measured VO2peak 42.13 mL min/kg). However, we would like to emphasise that Pianosi build his model on a patient population measured between 1991 and 1996, whereas, we used data from a 1996 to 2006 cohort. Within this different time frame, the quality of CF care has increased considerably due to progression in consensus and evidence-based medicine. This could have consequences for prognostic values of criteria, for example, the development of the FEV1 < 30%pred criterion, which indicated a median 2-year life expectancy based on a 1977–1989 cohort, while its expectancy increased to a median 5-year survival in a 1990–2003 cohort. This highlights the caution which should be taken in using the cut-off values reported in older literature, such as, for example, Pianosi et al.

With the prognostic value of exercise testing and especially VO2peak, annual follow-up of exercise capacity is important to identify individuals who are at risk for poorer prognosis, and identify those who may benefit from more intense therapy. However, a future study should also focus on the further validation of the developed model to predict VO2peak in patients with more advanced CF when more exercise-limiting mechanisms are involved. Furthermore, as some (variable) level of impairment in VO2peak is to be expected in patients with chronic conditions, it may be clinically helpful to interpret the achieved level of exercise capacity in comparison with what would be usual/expected given the patient’s age, gender and underlying diagnosis. Therefore, future studies should also focus on obtaining CF-specific reference values for cycle ergometer exercise testing as has been done for patients with other chronic conditions.

When using the reference equation to estimate VO2peak and in the absence of measured RER, we suggest to use a peak HR criterion of >180 bpm in adolescents beside the subjective signs, to asses whether an individual performed a maximal effort during cycling. Hence, care should be taken to consider a test as submaximal when the peak HR is below 180 bpm, as a ventilatory limitation can limit the HR to increase to maximal levels, as supported by previous work in our laboratory where we found significant lower peak HRs in adolescents with CF with evident static hyperinflation.

In conclusion, we have shown that peak work rate obtained using the Godfrey protocol and gender can be clinically used as a simple and valid alternative for the estimation of VO2peak in adolescents with CF in mild to moderate disease states in situations where it is not possible to formally measure VO2peak with gas analysis.

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Contributors All contributors (MW, EH, PH, BA and TT) substantially contributed to the design, planning and analysis of the study, and contributed substantially to the content of the manuscript.

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Competing interests None.

Ethics approval METC from the University Medical Centre Utrecht.

Provenance and peer review Not commissioned; externally peer reviewed.

Table 3 Prognostication based on measured versus predicted VO2peak

<table>
<thead>
<tr>
<th>Prognosis using measurement</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognosis using model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Medium</td>
<td>2</td>
<td>14</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>2</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>17</td>
<td>16</td>
<td>36</td>
</tr>
</tbody>
</table>

Figure 1 Bland–Altman plot of the predicted and measured VO2peak in the validation group.

Figure 2 Scatter plot of the predicted and measured VO2peak in the validation group.