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Estimating peak oxygen uptake in adolescents with cystic fibrosis

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ABSTRACT

Objectives To predict peak oxygen uptake (VO_{2peak}) from the peak work rate (W_{peak}) 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 ($FEV_{1\%pred}$) 86.82±17.77%), a regression equation was developed to predict VO_{2peak} (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 $FEV_{1\%pred}$ 85.43 ±20.01%).

Results We developed a regression model VO_{2peak} (mL/min)=216.3–138.7×sex (0=male; 1=female) +11.5×W_{peak}; R^2=0.91; SE of the estimate (SEE) 172.57. A statistically significant difference (107 mL/min; p<0.001) was found between predicted VO_{2peak} and measured VO_{2peak} 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 50–87% vs NPV 82–94%).

Conclusions In the absence of direct VO_{2peak} assessment it is possible to estimate VO_{2peak} 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.

What is already known on this topic

- Significant associations have been reported between exercise capacity and survival in patients with cystic fibrosis (CF).
- Many specialised CF centres still do not perform exercise testing, with or without gas analysis.
- Currently used field tests are not very strongly associated with VO_{2peak} in children and adolescents with CF.

What this study adds

- Even without gas analysis, it is possible to estimate peak oxygen uptake adequately in adolescents with cystic fibrosis using only a cycle ergometer.
- We found high positive predictive values and high negative predictive values for the model to assign individual patients to different prognosis clusters.

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 (VO_{2peak}),[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.[5] As mentioned previously, VO_{2peak} is a significant predictor of subsequent mortality, both as percentage of predicted[3 10] or as absolute value of mL min/kg.[4] Pianosi states that a VO_{2peak}<32 mL min/kg was associated with a 10-year mortality of 50%, whereas a VO_{2peak}>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 VO_{2peak} (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 VO_{2peak} 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 VO_{2peak} in children and adolescents with CF.[13]

The Godfrey protocol[14] is a validated cycle protocol to measure VO_{2peak} 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

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between VO_{2peak} and W_{peak} has been reported (coefficients of determination (R^2) 0.98±0.03) in healthy children[17] and in adolescents with CF ($r=0.91$; $p<0.001$).[18]

This might implicate that, theoretically, CPET using the Godfrey protocol measuring only W_{peak} (ie, without gas analysis) could provide an alternative and valid method for the prediction of VO_{2peak} 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 VO_{2peak} without gas analyses from W_{peak} on a cycle ergometer, using the Godfrey protocol in adolescents with CF and (2) assess the accuracy of this prediction model for prognostication clustering.

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 VO_{2peak} (mL/min).

Another 60 adolescents with CF (=validation group) also performed a CPET using the Godfrey protocol at their annual medical check-up. This group was used to validate the regression equation and to asses the accuracy of the model for prognostication 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 database 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 exercise data of the patients in the database who performed a maximal effort ($HR_{peak}>180$ bpm,[21] $RER_{peak}>1.0$ and subjective signs of voluntary exhaustion. For a maximal effort, participants had to meet all the criteria.[9]

Godfrey exercise protocol

The Godfrey protocol was performed on an electronically braked cycle ergometer (Lode Corrival, Procare 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, Lummen, Belgium). Expired gas passed through a flow metre, oxygen analyser, and a carbon dioxide analyser. The flow metre and gas analyser were connected to a computer, which calculated breath-by-breath minute ventilation (VE), oxygen uptake (VO_2), carbon dioxide production (VCO_2), and respiratory exchange ratio (RER) from conventional equations. Heart rate (HR) was also monitored continuously by a 12-lead electrocardiogram (Cardioperfect, Accuramed Bv, Lummen, Belgium), and transcutaneous oxygen saturation (SpO_2%) 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 V.17.0 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 VO_{2peak} (mL/min) based on the W_{peak} combined with standard anthropometric variables based on biological plausibility (height (cm), age (years), sex (0=male; 1=female) and lung function (FEV_1 (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 prognostication clustering. Paired sample t tests or Wilcoxon signed ranks tests were used to analyse possible differences between actual and predicted VO_{2peak}. A Bland–Altman plot was used to assess any systematic bias between measured VO_{2peak} and predicted VO_{2peak}. 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 VO_{2peak} of the participants 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) VO_{2peak} 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 $FEV_{1\%pred}$ 86.82±17.77%) were tested in our laboratory between 1996 and 2006.The characteristics of the reference group are presented in table 1.

Prediction of the VO_{2peak} from the W_{peak}

Linear regression revealed the following equation (95% prediction interval between 1770 and 2548 mL/min), with W_{peak} and sex as the only significant contributors (see table 2).

$$VO_{2peak}(\text{mL/min}) = 216.3 - 138.7 \times \text{Sex}(0 = \text{female}/1 = \text{male}) + 11.5 \times W_{peak}$$

The greatest contributor to this regression equation was W_{peak} 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 FEV_1 (β=0.03; p=0.34) did not make a significant additional contribution.

Cross-validation

All 60 participants in the validation group successfully performed CPET without complications or adverse events. Descriptive characteristics are presented in table 1.

Table 1 Patient characteristics and peak exercise data

	Reference group (n=363)	Validation group (n=60)
Age (years)	14.77±1.73 [12.08–18.33]	14.58±1.67
Weight (kg)	51.31±11.39 [30.10–94.60]	50.44±9.68
Height (cm)	164.20±10.75 [134.80–190.10]	165.29±11.92
Sex	223 females 140 males	28 females; 32 males
FEV_1% predicted (FEV_1 (L))	86.82±17.77 (2.72±0.82) [37–147]	85.43±20.01 (2.71±.94)
HR_{peak} (bpm)	190±7 [180–210]	180±12
RER_{peak}	1.2±0.1 [1.0–1.7]	1.13±0.11
W_{peak} (watt)	174±45 [75–300]	171±46
VO_{2peak} (mL/min)	2151±571 [1000–3800]	2019±567

HR, heart rate; RER, respiratory exchange ratio.

Based on previous mentioned criteria, 36 performed a maximal effort (20 female and 16 male, age 14.6±1.7 years, $FEV_{1\%}$ 86.89±18.67%, HR_{peak} 188±7 bpm, RER_{peak} 1.16 ±0.08). Their data were used to calculate the differences between measured and predicted VO_{2peak}.

We found a small but statistically significant difference (mean difference 107 mL/min; $p<0.01$) between predicted VO_{2peak} (2231±550 mL/min) and measured VO_{2peak} (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 W_{peak} (standardised β=0.83; $p<0.001$) and sex (standardised β=−0.17; p=0.038) as the only significant contributors:

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

Prognostics

The positive predictive values for the model to correctly assign patients to the low, medium or high VO_{2peak} 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 VO_{2peak} were 86%, 82% and 94%, respectively (see table 3).

DISCUSSION

The objectives of this study were (1) to predict VO_{2peak} from W_{peak} 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 VO_{2peak} (mL/min) out of W_{peak} and sex in a group of adolescents with CF with a large range in pulmonary function ($FEV_{1\%pred}$ (37–147%)) 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 VO_{2peak} and W_{peak} (coefficients of determination (R^2) 0.98±0.03) in healthy children[17] and in children with CF (r=0.91; $p<0.001$).[18] However, the slope of the VO_2 as response to the work-rate increment ($\Delta O_2/\Delta W$) was higher in children with CF compared with healthy controls.[17] This could suggest a high oxygen consumption of the respiratory muscles by a higher work of breathing in patients with lung disease.[22 23] In patients with CF, especially in a more severe disease status, several mechanisms become involved, such as an increased work of breathing during exercise.[2]

Although we observed statistically significant differences between the predicted VO_{2peak} and the measured VO_{2peak} 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 VO_{2peak} was smaller than the SE of measurement (SEM 138 mL/min (8.5%)) in a test-retest reliability study of VO_{2peak} in adult patients with CF in a severe disease status (mean FEV_1 52% of predicted, age 26.9±6.0).[23] Linear regression analysis in the validation group with VO_{2peak} 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, W_{peak} from the Godfrey protocol and sex may serve as clinical valid predictors of VO_{2peak} 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 2 Final regression model

Final regression model	R	R^2	SEE	p Value	95% PI
	0.954	0.909	172.57	<0.001	(1770–2548)
Outcome variable	**Predictor variable**	**Unstandardised β**	**Standardised β**	**95% CI**	**p Value**
VO_{2peak} (mL/min)	Constant	216.342		128.360 to 304.324	<0.001
	Sex	−138.713	−0.118	−180.004 to −97.423	<0.001
	W_{peak}	11.445	0.897	10.996 to −11.895	<0.001

SEE, SE of the estimate.

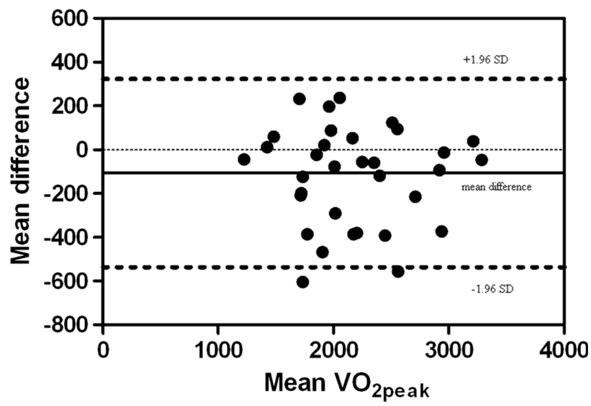

Figure 1 Bland–Altman plot of the predicted and measured VO_{2peak} in the validation group.

Table 3 Prognostication based on measured versus predicted VO_{2peak}

	Prognosis using measurement			
	Low	Medium	High	Total
Prognosis using model				
Low	1	1	0	2
Medium	2	14	3	19
High	0	2	13	15
Total	3	17	16	36

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 (VO_{2peak}<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).[24] As Pianosi *et al* found a VO_{2peak}<32 mL min/kg to be associated with a 10-year mortality of 50%, and a VO_{2peak}>45 mL min/kg to be associated with a 10-year mortality of 0%, the mean difference in VO_{2peak} of our model (107 mL/min) is also quite accurate in a prognostic point of view.[24] In our validation group with a mean weight of 50.44 kg, the difference in VO_{2peak} between 'good' and 'bad' prognostic groups would be 655.7 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 1770 (~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 VO_{2peak} and estimated VO_{2peak} were both within the same prognosis cluster of Pianosi *et al* (predicted VO_{2peak} 44.23 mL min/kg vs measured VO_{2peak} 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.[25 26] This could have consequences for prognostic values of criteria, for example, the development of the FEV_1<30%$_{pred}$ criterion, which indicated a median 2-year life expectancy based on a 1977–1989 cohort,[27] while its expectancy increased to a median 5-year survival in a 1990–2003 cohort.[25] 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*.

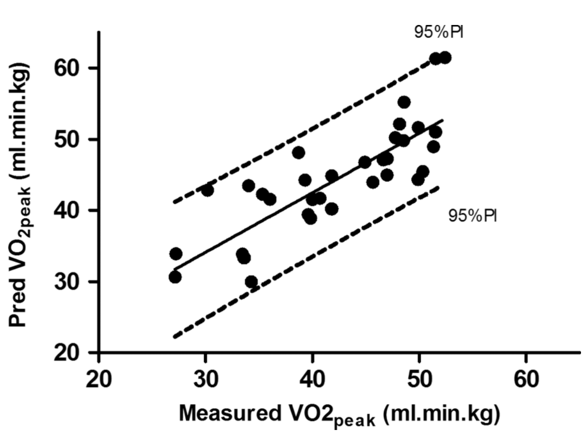

Figure 2 Scatter plot of the predicted and measured VO_{2peak} in the validation group.

With the prognostic value of exercise testing and especially VO_{2peak}, 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.[28] However, a future study should also focus on the further validation of the developed model to predict VO_{2peak} in patients with more advanced CF when more exercise-limiting mechanisms are involved. Furthermore, as some (variable) level of impairment in VO_{2peak} 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.[29] 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.[29 30]

When using the reference equation to estimate VO_{2peak}, 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.[21] 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.[31]

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 VO_{2peak} in adolescents with CF in mild to moderate disease states in situations where it is not possible to formally measure VO_{2peak} with gas analysis.

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Competing interests None.

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