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Original Article

Towards an individualized protocol for workload increments in cardiopulmonary exercise testing in children and adolescents with cystic fibrosis

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Abstract

Background: There is no single optimal exercise testing protocol for children and adolescents with cystic fibrosis (CF) that differs widely in age and disease status. The aim of this study was to develop a CF-specific, individualized approach to determine workload increments for a cycle ergometry testing protocol.
Methods: A total of 409 assessments consisting of maximal exercise data, anthropometric parameters, and lung function measures from 160 children and adolescents with CF were examined. 90% of the database was analyzed with backward linear regression with peak workload (W_{peak}) as the dependent variable. Afterwards, we [1] used the remaining 10% of the database (model validation group) to validate the model's capacity to predict W_{peak} and [2] validated the protocol's ability to provide a maximal effort within a 10±2 minute time frame in 14 adolescents with CF who were tested using this new protocol (protocol validation group).
Results: No significant differences were seen in W_{peak} and predicted W_{peak} in the model validation group or in the protocol validation group. Eight of 14 adolescents with CF in the protocol validation group performed a maximal effort, and seven of them terminated the test within the 10±2 minute time frame. Backward linear regression analysis resulted in the following equation: W_{peak} (W) $= -142.865 + 2.998 \times$ Age (years) $- 19.206 \times$ Sex (0=male; 1=female) $+ 1.328 \times$ Height (cm) $+ 23.362 \times FEV_1$ (L) (R=.89; R^2=.79; SEE=21). Bland–Altman analysis showed no systematic bias between the actual and predicted W_{peak}.
Conclusion: We developed a CF-specific linear regression model to predict peak workload based on standard measures of anthropometry and FEV_1, which could be used to calculate individualized workload increments for a cycle ergometry testing protocol.

Keywords: Exercise capacity; Cycle ergometer protocol; Peak workload

1. Introduction

The clinical utility of exercise and exercise testing in the diagnosis and treatment as well as the primary and secondary prevention of chronic conditions is widely recognized by health care professionals. This is evidenced by the fact that cardiopulmonary exercise testing (CPET) is increasingly used to evaluate exercise capacity and define training intensity in adolescents with chronic lung diseases like cystic fibrosis (CF) [1,2]. Numerous protocols have been used in the past to evaluate physical fitness in adolescents with chronic conditions, but there is still no consensus with regards to the best protocol to be used in the clinical setting. Moreover, there is some question as to whether these exercise testing protocols should vary by pediatric condition or even between patients with the same condition. Ultimately, the characteristics of the patient and the purpose of the exercise test will determine which protocol is most suited for each individual patient. Aside

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from patient characteristics, it has been suggested that the length of the exercise test represents an additional important criterion to consider when designing a protocol that will elicit maximal or peak oxygen uptake and demonstrate good reproducibility of commonly measured exercise parameters (e.g. ventilatory threshold). While a test duration of 10 ± 2 min has been recommended to allow the patient to reach their limit of tolerance [3,4]. Midgley et al. nuanced this recommendation by suggesting that cycle ergometer tests should last between 7 and 26 min with a focus on tolerable workload increments rather than test duration, per se [5].

Progressive incremental cycle ergometer protocols, continuous incremental (ramp) protocols, and protocols with short stage duration (e.g. 1 min) are very efficient at inducing maximal exercise responses in an optimal time frame (~10 to 12 min). The Godfrey protocol was the first 1-minute incremental protocol systematically used in pediatric CF patients [6,7]. This protocol separates subjects into 3 groups based on height with workload increments increasing with height from 10 W to 15 W and 20 W per min. The large differences in disease severity and the progressive nature of CF make a more individualized approach to the incremental exercise test critical. It is generally accepted that, to date, there is no single best exercise testing protocol to answer all questions in individuals with CF with a wide range of ages and disease states [8,9]. Therefore, we aimed to develop a CF-specific, individualized approach from standard measures of anthropometry and lung function in children and adolescents to determine workload increments for a maximal cycle exercise test.

2. Methods

Maximal effort cycle ergometer CPET data (n = 409) from 160 children and adolescents with CF receiving care at the Cystic Fibrosis Center of the Wilhelmina Children's Hospital, Utrecht, the Netherlands, were analyzed. Body weight, height, lung function and exercise capacity were determined as part of routine measures at the patient's annual medical check-up. Since all measurements were a part of patient standard of care, ethical approval and informed consent were not required according to Dutch Law.

Out of the database, a regression model was developed out of 90% of the data (reference group). Afterwards, we [1] used the remaining 10% of the database (model validation group) to validate the model's capacity to predict W_{peak} and [2] validated the protocol's (minute increment = predicted $W_{peak}/10$) ability to provide a maximal effort within a 10 ± 2 minute time frame in 14 adolescents with CF who were tested using this new protocol (protocol validation group). The CPET was part of their usual care at the annual CF check-up.

2.1. Spirometry

Spirometry and body plethysmography were performed before and after bronchodilation with salbutamol (800 µg), using a pneumotach apparatus and a volume-constant plethysmograph (Master Lab system, E. Jaeger, Würzburg, Germany). Lung function measurements included total lung capacity (TLC), residual volume (RV), and forced expiratory volume in 1 s (FEV_1). These results were compared with predicted values for healthy subjects matched for age, height, and gender [10].

2.2. Cardiopulmonary exercise test (CPET)

After bronchodilation with salbutamol, all participants performed a progressive cardiopulmonary exercise test (CPET) on an electronically braked cycle ergometer (Jaeger physis; Carefusion, Houten, The Netherlands) to assess exercise capacity. Ergometer seat height was adjusted to the participant's comfort and leg length. Participants rested until all measured variables were stable, and then began cycling at a workload of 0 W; the workload was increased 15 W/min until the participant stopped due to volitional exhaustion. Throughout the exercise, participants breathed through a mask (Hans Rudolph Inc., Kansas City, MO) that was connected to a calibrated metabolic cart (Oxycon Pro, Carefusion, Houten, The Netherlands). Expired gas was passed through a flow meter, oxygen analyzer, and carbon dioxide analyzer, which were connected to a computer that 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 was monitored continuously by 3-lead electrocardiography (Hewlett-Packard, Amstelveen, Netherlands). The oxygen uptake and workload completed in the final 30 s prior to exhaustion were considered to be VO_{2peak} and W_{peak}, respectively. Relative peak oxygen uptake (VO_{2peak}/kg) was calculated by dividing VO_{2peak} by total body mass. All participants included in the analysis were required to have performed a maximal effort test, which was defined by a combination of subjective and objective criteria. Subjective criteria included subject exhaustion (unsteady biking, sweating, facial flushing) or an inability to maintain the required cadence of 60 rpm despite strong verbal encouragement. Objective criteria included: (1) peak heart rate (HR_{peak}) > 180 bpm [11] and (2) respiratory exchange ratio (RER) > 1.00. Based on previous literature, a true maximal effort required participants to demonstrate both objective and subjective criteria [12].

2.3. Statistics

All variables were tested for normality with the Kolmogorov–Smirnov test. Backward linear regression analysis was performed using the data of the reference group. Peak workload (W_{peak}) was defined as the dependent variable in the model, while gender, height, and FEV_1 (L) were selected as independent variables. The model validation group was used to validate the models capacity to predict W_{peak}. Student's t-tests or Mann–Whitney test was used to assess differences between the reference and validation groups for gender distribution, height, weight, $FEV_{1\%pred}$, W_{peak} and VO_{2peak}. For the model validation group, a Bland–Altman plot was used to assess any systematic bias between actual W_{peak} and W_{peak} predicted. After developing the regression equation, we validated the new protocol in the protocol validation group.

Statistical significance was set at $p<0.05$. All statistical analyses were performed in SPSS 15.0 for Windows (Chicago, IL, USA).

3. Results

Kolmogorov–Smirnov tests revealed that FEV_1 (L), W_{peak}, HR_{peak}, RER_{peak} and time to exhaustion (Tlim) were not normally distributed. However, the residuals of the model predicting W_{peak} were normally distributed. No complications were observed during or after exercise testing.

RER_{peak} of the total group was 1.19±0.09 [range 1.0–1.67] and HR_{peak} 190±7 [range 180–210] beats per minute (bpm). No differences in maximal exercise parameters were found between both groups (reference group RER_{peak} 1.20±0.09 [range 1.0–1.67] and HR_{peak} 189±7 [range 180–210 bpm] versus model validation group RER_{peak} 1.18±0.09 [range 1.0–1.45] and HR_{peak} 190±6 [range 180–210 bpm]; p=.33 for RER_{peak} and HR_{peak}).

Anthropometric characteristics of both groups are presented in Table 1. Mean $FEV_{1\%pred}$ for the validation and reference groups was 86.9±19.3% and 87.2±17.4% (p=.91), respectively. Gender distribution between the reference and validation group was similar (38% ♀ and 62% ♂ in the reference group vs. 45% ♀ and 55% ♂ in the validation group; X^2 test p=.503). No differences in age were seen between the validation and regression group (14.2±1.9 [11–18] vs. 14.5±2.0 [8–18] years; p=.41).

For the reference group, mean W_{peak} was 171.2±46.3 W with a mean Tlim of 11.4 min [range 5.0–20.0 min]. For the model validation group, mean W_{peak} was 164.6±38.6 W, and mean Tlim was 11.0 min [range 7.0–16.0 min]. No differences were noted for W_{peak} (p=.496) or Tlim (p=.496) between the reference and model validation groups.

Height, weight, FEV_1 (L and %predicted), gender, and age were all significantly associated with W_{peak} (.319–.803; p<.001) in pediatric patients with CF, with the strongest correlation found for FEV_1 (L) (*r* .803; p<.001) (see Table 2).

Inclusion of these variables in backward linear regression analysis resulted in the following equation:

$$\begin{aligned} W_{peak}(W) = {} & -142.865 + 2.998 \times Age\ (years) - 19.206 \\ & \times Sex\ (0 = male;\ 1 = female) + 1.328 \\ & \times Height\ \ (cm) + 23.362 \times FEV_1\left(L{\cdot}min^{-1}\right) \end{aligned}$$

$$R = .89;\ R^2 = .79;\ SEE = 21.0.$$

Extrapolating this equation to the model validation group resulted in a predicted mean W_{peak} of 164.6±38.6 W, compared with the actual mean W_{peak} of 166.5±38.1 (p=.09).

Table 1
Anthropometric values.

	Age	Gender	Weight	Height	FEV_{1pred}
Reference group	14.5±2.0	17♀ 21♂	50.0±12.2	162.6±12.0	87.2±17.4
Validation group	14.2±1.9	140♀ 231♂	49.1±9.9	161.9±11.1	86.9±19.3

Table 2
Correlation coefficients for weight, age and lung function with W_{peak} in males and females.

		W_{peak}
Pearson correlation	Age	.64
	Sex	−.42
	Weight	.78
	FEV_{1pp}	.32
	Height	.80

Bland–Altman analysis showed no systematic bias between the actual and predicted W_{peak} (see Fig. 1).

Based on these findings, we conclude that the model developed in the present study to predict W_{peak} from standard anthropometric variables is valid. Ultimately, this approach will provide more optimal CF-specific exercise testing of comparable test duration across a wide variety of ages and disease states.

We validated the developed protocol (increments per minute= predicted $W_{peak}/10$) in 14 adolescents with CF. Six of them were excluded from further analysis while they did not meet the above mentioned criteria for maximal effort. The remaining eight participants (3 female, 5 male; age 15.6±2.2 years [12–19]; FEV_1 3.0±0.8 L; $FEV_{1\%pred}$ 87±19%; height 167±10 cm; weight 52±9 kg) were used to validate the protocol (Tlim 10.8±1.4 min [9.2–13.3 min]; RER_{peak} 1.28±0.06 [range 1.21–1.40] and HR_{peak} 185±4 [range 181–189 bpm]). Seven of them performed a maximal effort within the targeted 10±2 minute time frame.

When we compare the Tlim of the CF-specific protocol with the estimated Tlim of the Godfrey protocol ($W_{peak}/20$ W per min), much more variance in Tlim would have been found in the Godfrey protocol (95% CI for CF specific protocol 9.7–12.0 min versus 7.8–12.0 min) (see Fig. 2).

We found no difference between measured W_{peak} and estimated W_{peak} (197±50 W versus 186±38 W; p=.22). Bland–Altman

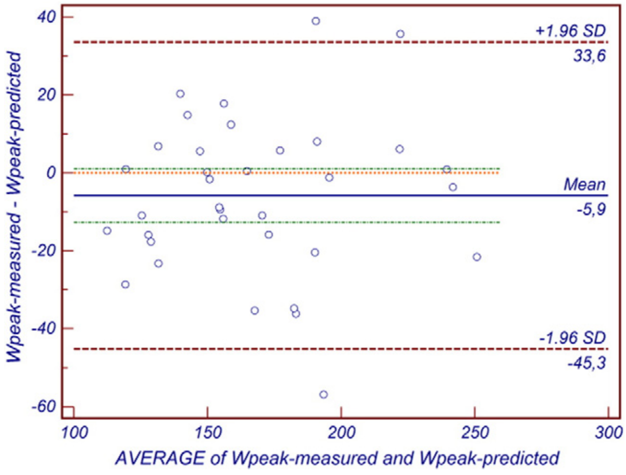

Fig. 1. Bland–Altman plot of the measured W_{peak} and predicted W_{peak} in the model validation group showing the bias and limits of agreement. Bland–Altman plot has been developed from the 10% validation group.

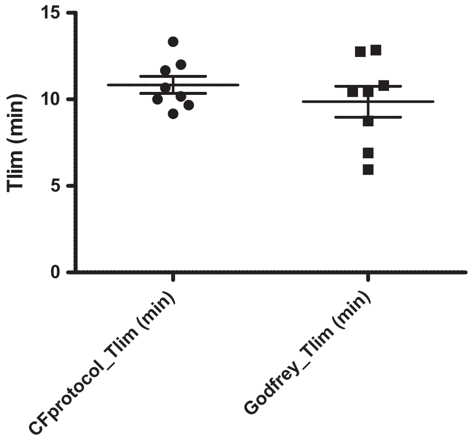

Fig. 2. Vertical point plot of the mean Tlim (95% CI) of both protocols.

analysis showed no systemic bias between actual and predicted W_{peak} (mean difference 10.9 W; LOA+55.7; −33.9 W) (see Fig. 3).

4. Discussion

We aimed to develop a CF-specific linear regression model for children and adolescents to predict peak workload based on standard measures of anthropometry and FEV_1, which could then be used to calculate individualized workload increments for an exercise protocol wherein participants achieve cardiopulmonary exhaustion in approximately 10 min. While an individualized exercise protocol has previously been shown to be feasible in children and adolescents with various diseases, it is important to note that in that study the individualization was based on peak oxygen uptake rather than peak workload [13]. In the current study, height, weight, FEV_1, gender and age were significantly associated with W_{peak} in adolescent patients with CF. Given the strength of the relationship between W_{peak} and height, it seems that the exercise protocol developed by Godfrey, who based the increments on the individual's height (10 W/min < 120 cm; 15 W/min 120–150 cm; 20 W/min > 150 cm), already provides better individualization of the exercise increments for children and adolescents (with CF) than standard increments.

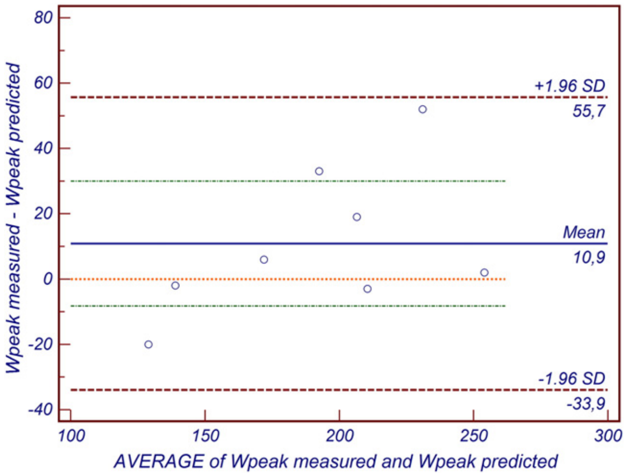

Fig. 3. Bland–Altman plot of the measured W_{peak} and predicted W_{peak} in the protocol validation group.

Generally, a workload increment that brings the subject to their limit of tolerance in about 10 min is suggested to provide optimal cardiopulmonary assessment [4]. Despite the grading of the workload increments according to size in the Godfrey protocol, the smallest healthy children and adolescents complete the test in about 4 min, whereas tests for the largest healthy children last roughly 10 min [7]. The preliminary termination seen in small children and adolescents may be due to workload increments that are too large, resulting in premature exhaustion of the muscles of the lower limbs before the attainment of cardiac or respiratory limits [13]. Additionally, VO_2 on-kinetics are reportedly slowed in steeper ramp slopes, [14] which may compromise the aerobic contribution to total energy delivery [14] and lead to premature exhaustion of the anaerobic energy system in the local muscles. Therefore, at least in smaller children and adolescents, as is the case in CF, a protocol based solely on a single variable such as height does not seem to provide the appropriate workload increments to achieve VO_{2peak} in the suggested 10-minute time frame.

Conversely, a multivariable-based exercise protocol may allow for better selection of workload increments leading to more optimal exercise duration. Linear regression analysis showed gender, FEV_1, age and height to be significant and independent predictors of W_{peak}. The resulting model explained 79% of the variance in W_{peak}. Validation of the models' capacity to predict W_{peak} showed no significant difference between the measured W_{peak} and estimated W_{peak} in a sample of children and adolescents with CF. Moreover, Bland–Altman analysis showed no systematic bias between the measured W_{peak} and estimated W_{peak}. Additionally, we validated the new incremental protocol and found no difference between measured W_{peak} and estimated W_{peak} (197 ± 50 W versus 186 ± 38 W; p = .22), whereas the maximal effort was performed within the targeted 10 ± 2 minute time frame in seven of the eight participants who performed a maximal effort.

To ensure a maximal effort, we used previously used modified criteria in our laboratory [12]. The achievement of these criteria was of critical importance as questions about cardiopulmonary limiting factors or cardiopulmonary exercise capacity can only be answered when the cardiopulmonary system has truly reached its limitations. Individualization of the exercise protocol has been shown to provide achievement of the maximal exercise criteria in approximately 10 minute exercise duration in a higher proportion of children and adolescents [13].

Based on these findings, we conclude that the model developed in the present study to predict W_{peak} from standard anthropometric variables is valid. Dividing the predicted W_{peak} by 10 to determine individualized workload increments for the maximal exercise test will allow participants to achieve true cardiopulmonary exhaustion in the recommended 10-minute time frame. Ultimately, this approach will provide more optimal CF-specific exercise testing of comparable test duration across a wide variety of ages and disease states. However, the equation has not been tested or validated in adult patients with CF. Further research to cross-validate this individualized protocol in adolescents and adults with CF is suggested. Additionally, CF-specific normative data for W_{peak} are required for the interpretation of the test results.

Conflicts of interest

The authors declare that they have no financial or personal relationship to disclose with regards to the current study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcf.2012.05.004.

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