Pediatric exercise testing

In health and disease

Colophon

Pediatric exercise testing: in health and disease
Thesis, Utrecht University, Utrecht, the Netherlands, with a summary in Dutch
Proefschrift, Universiteit Utrecht, Utrecht, met een Nederlandse samenvatting

ISBN 978 90 5291 111 3
Universitaire Pers Maastricht

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Cover design and lay-out: Datawyse | www.datawyse.nl
Printed by: Universitaire Pers Maastricht

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Financial support by the Division of Pediatrics of the University Medical Center Utrecht, Lode BV, ProCare BV, and Samcon BVBA for the publication of this thesis is gratefully acknowledged.

Pediatric exercise testing
In health and disease

Het uitvoeren van inspanningstesten bij kinderen
In gezondheid en bij ziekte

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op
dinsdag 23 april 2013 des ochtends te 10.30 uur

door

BART CHATEAU BONGERS
geboren op 25 oktober 1985 te Geleen, Limburg

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"*Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save it and preserve it.*"

Plato, 350 B.C.

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Contents

List of abbreviations

ΔOMNI	Post-test OMNI score minus pre-test OMNI score
ΔVAS	Post-test visual analog scale score minus pre-test visual analog scale score
∑4SF	Sum of the four skin folds
ANOVA	Analysis of variance
BF	Breathing frequency
BF%	Body fat percentage
BMI	Body mass index
BSA	Body surface area
$(CaO_2 - CvO_2)_{max}$	Maximal arteriovenous difference in oxygen content
CF	Cystic fibrosis
CHD	Congenital heart disease
CI	Confidence interval
CO_{max}	Maximal cardiac output
CPET	Cardiopulmonary exercise testing
ECG	Electrocardiogram
FEV_1	Forced expiratory volume in one second
FFM	Fat free mass
FVC	Forced vital capacity
GAMLSS	Generalized additive models for location, scale, and shape
HIT	High-intensity interval exercise training
HR	Heart rate
HR_{peak}	Peak heart rate
ICC	Intraclass correlation coefficient
LMS	Least mean square
Log $\dot{V}E$	Common logarithm of the minute ventilation
LSD	Least significant difference
LV	Left ventricle
MSEC	Maximal short-time exercise capacity
NA	Not applicable
NS	Not significant
OUE	Oxygen uptake efficiency
OUEP	Oxygen uptake efficiency plateau
OUES	Oxygen uptake efficiency slope
OUES/BSA	Oxygen uptake efficiency slope normalized for body surface area
PA	Physical activity

PAR-Q	Physical activity readiness questionnaire
$P_{ET}CO_2$	Partial end-tidal carbon dioxide tension
$P_{ET}O_2$	Partial end-tidal oxygen tension
RER	Respiratory exchange ratio
RER_{peak}	Peak respiratory exchange ratio
ROC	Receiver operator characteristic
RV	Residual volume
RV/TLC%	Ratio of the residual volume to the total lung volume
SD	Standard deviation
SEE	Standard error of the estimate
SRT	Steep ramp test
SpO_2	Peripheral oxygen saturation
SpO_{2peak}	Peripheral oxygen saturation at peak exercise
TAP	Transannular patch
TGA	Transposition of the great arteries
TLC	Total lung volume
ToF	Tetralogy of Fallot
TV	Tidal volume
V_D/V_T ratio	Ventilatory dead space ventilation
VAS	Visual analog scale
V_{CO_2}	Carbon dioxide production
V_E	Minute ventilation
$V_{E_{peak}}$	Peak minute ventilation
V_E/V_{CO_2}-slope	Relationship between the minute ventilation and the carbon dioxide production
V_E/V_{O_2}-slope	Relationship between the minute ventilation and the oxygen uptake
V_{O_2}	Oxygen uptake
$V_{O_{2max}}$	Maximal oxygen uptake
$V_{O_{2peak}}$	Peak oxygen uptake
VSD	Ventricular septal defect
VT	Ventilatory threshold
VT%	Ventilatory threshold expressed as a percentage of peak oxygen uptake
WAnT	Wingate anaerobic test
WR	Work rate
WR_{peak}	Peak work rate

General introduction

Aerobic exercise capacity and health

Childhood and adolescence are crucial periods in life, since remarkable physiological and psychological changes take place throughout these periods, due to growth and maturation, thereby influencing physical fitness. Physical fitness can be considered as an integrated measure of most, if not all, body functions involved in the performance of daily physical activity and physical exercise.[1] These body functions include aerobic exercise capacity, body composition, muscular strength, power, speed, balance, flexibility, and hand-eye coordination.[2] Pediatric exercise testing is a valuable, non-invasive procedure to evaluate physical fitness throughout childhood and adolescence. Traditionally, pediatric exercise testing has focused on the cardiopulmonary system by measuring aerobic exercise capacity.*[3] Nowadays, physical fitness has even become synonymous with aerobic exercise capacity.

Aerobic exercise capacity is defined as the ability to perform dynamic, moderate- to high-intensity exercise, involving large muscle groups, for prolonged periods of time.[4] It is an important determinant of overall health, in which a higher aerobic exercise capacity is related to a lower morbidity and mortality in healthy adults,[5,6] as well as in adult patients.[7] In children and adolescents, aerobic exercise capacity has also been reported to be an important marker of health.[1] For example, higher aerobic exercise capacity is associated to lower total adiposity,[8] and is inversely associated to cardiovascular risk factors.[9] This highlights the importance of pediatric exercise testing for health screening purposes in childhood and adolescence. For children and adolescents with a chronic condition, maintaining or increasing aerobic exercise capacity is at least of equal importance.[10] In the Netherlands, fourteen to twenty percent of all children (546,000 – 780,000) have a chronic condition, ranging from a mild condition such as bronchitis to a severe condition such as a congenital heart disease.[11] The chronic condition itself often causes hypoactivity, which results in a reduction in the functional ability of the child, and thus further hypoactivity (see FIGURE 1).[12] Many children with a chronic condition have a reduced aerobic exercise capacity,[13] and this negative feedback loop can occur in any child with a chronic condition.[12] Exercise training programs in children with a chronic condition have been shown to be effective in improving aerobic exercise capacity.[14-17]

* Synonyms for aerobic exercise capacity are aerobic fitness, aerobic capacity, cardiopulmonary fitness, and cardiopulmonary exercise capacity.

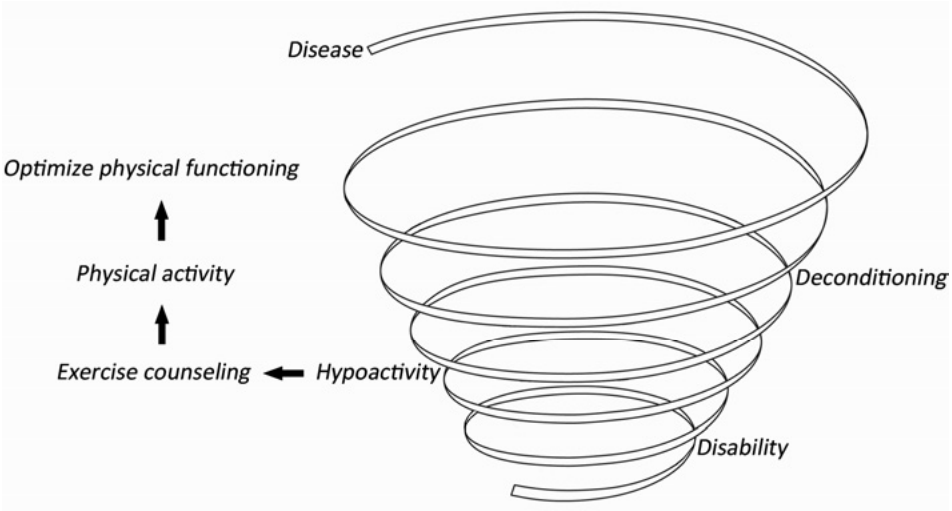

FIGURE 1. The relationship between disease, deconditioning, inactivity, and disability.

NOTE: adapted from Painter.[18]

Cardiopulmonary exercise testing

A child's aerobic exercise capacity can be accurately evaluated during progressive cardiopulmonary exercise testing (CPET), involving large muscle groups (e.g. cycle or treadmill ergometry), up to maximal exertion. The work rate (WR) during CPET increases progressively in order to achieve maximal exertion within six to ten minutes in children,[19] and within eight to twelve minutes in adolescents.[20] Traditionally, CPET was indicated for the provocation of cardiac arrhythmias, the assessment of myocardial ischemia, and the assessment of exercise-induced bronchoconstriction. Nowadays, CPET also serves an important role in evaluating the physiological responses to exercise in children with an extensive range of endocrine, musculoskeletal, metabolic, neurologic, immunologic, cardiac, and pulmonary diseases.[21] Specific indications for pediatric CPET are listed in TABLE 1.

Throughout CPET, respiratory gas analysis measurements are performed, in combination with an electrocardiogram (ECG), blood pressure measurements, and oxygen saturation measurements (see APPENDIX). Therefore, CPET can be utilized to assess the integrative physiological response of the pulmonary, cardiovascular, hematopoietic, and metabolic systems throughout progressive exercise up to maximal exertion, and during recovery in a controlled laboratory environment. It

evaluates the integrated function of multiple organ systems to meet the increased cellular respiratory demands of the exercising muscles during submaximal and maximal exercise. Specifically, it evaluates the increased need for oxygen and the removal of metabolically produced carbon dioxide. This non-invasive and dynamic assessment of the physiological response to submaximal and maximal exercise provides the clinician with important information for clinical decision making.[22] More precisely, the results of CPET can be appreciated in (support of) diagnostics, assessment of disease severity, prognosis, and response to an intervention. CPET has gained popularity due to its additive value, and is being increasingly utilized in daily (clinical) practice.[22-27]

Measuring maximal oxygen uptake ($V\text{O}_{2\text{max}}$) during progressive CPET, that involves large muscle groups (e.g. cycle or treadmill ergometry) up to maximal exertion, is considered the gold standard for assessing aerobic exercise capacity by the World Health Organization,[28] as well as by others.[22,23,29] $V\text{O}_{2\text{max}}$ is defined as the maximal capacity of the pulmonary and cardiovascular system to take up and transport oxygen to the exercising muscles, and of the exercising muscles to extract and utilize oxygen from the blood (see FIGURE 2).[27] Each of the systems involved in the pathway for oxygen from the atmosphere to the mitochondria might be a physiological limiting factor for $V\text{O}_{2\text{max}}$. These physiological limiting factors include pulmonary diffusing capacity, cardiac output, oxygen carrying capacity of the blood, and oxygen extraction, as well as oxygen utilization capacity of the exercising muscles. Pulmonary diffusing capacity depends on ventilation, ventilation-perfusion matching, pulmonary diffusing capacity, and the binding affinity of hemoglobin for oxygen.[30] Cardiac output is the product of heart rate (HR) and left ventricular stroke volume. Factors that can influence the oxygen carrying capacity of the blood are the available hemoglobin, arterial oxygen saturation, and oxygen dissociation curve shifts with temperature, carbon dioxide, and pH.[22] Oxygen extraction and oxygen utilization capacity of the exercising muscles depend on capillary density, adequacy of perfusion, and tissue diffusion.[22] Moreover, the amount of sufficiently working mitochondria in the exercising muscles to meet the energy requirements, as well as the amount of enzymes and intermediate products necessary to sustain the rate of energy production, are potential limiting factors.[31] The Fick equation combines the above defined physiological limiting factors for $V\text{O}_{2\text{max}}$[32]:

$$V\text{O}_{2\text{max}} = \text{CO}_{\text{max}} \times (\text{Ca}\text{O}_2 - \text{Cv}\text{O}_2)_{\text{max}}$$

where '$V\text{O}_{2\text{max}}$' is the maximal oxygen uptake ($\text{mL}\cdot\text{min}^{-1}$), '$\text{CO}_{\text{max}}$' stands for maximal cardiac output ($\text{mL}\cdot\text{min}^{-1}$), which depends on the HR at peak exercise (HR_{peak}; $\text{beats}\cdot\text{min}^{-1}$) and the left ventricular stroke volume at peak exercise (mL), and

'$(Ca{O_2} - Cv{O_2})_{max}$' represents the maximal arteriovenous difference in oxygen content (mL). The latter is associated with the pulmonary diffusing capacity, as well as with the maximal ability of the exercising muscles to extract and utilize oxygen from the blood. Another factor that influences $V{O_{2max}}$ is body size. Much of the age-related increase in absolute $V{O_{2max}}$ values throughout childhood reflects an overall increase in body size. The most commonly used method to normalize for differences in body size is to divide absolute $V{O_{2max}}$ values ($mL \cdot min^{-1}$) by body mass ($mL \cdot kg^{-1} \cdot min^{-1}$).[22,33]

TABLE 1. Indications for pediatric CPET.

Cardiopulmonary exercise testing as a diagnostic test
Assessment of aerobic exercise capacity (VO_{2max}/VO_{2peak})
Assessment of exercise limiting factors, including pathophysiological changes
Assessment of heart rhythm and heart rate
Assessment of blood pressure response
Assessment of exercise-induced bronchoconstriction or dysfunctional breathing
Assessment of exercise-induced symptoms (chest pain, dyspnea, increased fatigability)
Cardiopulmonary exercise testing for the assessment of disease severity
Heart disease:
Assessment of exercise-induced arrhythmias and repolarization disturbances
Assessment of myocardial ischemia
Assessment of the efficacy of a surgical correction
Assessment and optimization of pacemaker function
Respiratory disease:
Assessment of gas exchange abnormalities
Assessment of overall pulmonary gas exchange
Assessment of hypoxia
Assessment of lung transplantation
Cardiopulmonary exercise testing as a prognostic test
Assessment of the course of a progressive disease (regular follow-up)
Assessing other (additional) potential contributing factors to exercise limitation
Cardiopulmonary exercise testing as an evaluative test
Assess suitability and establish a baseline before beginning an intervention program
Pre-operative or pre-treatment screening (e.g. lung transplantation, chemotherapy)
Assessment of the effectiveness of an intervention program
Assessment of the effects of medication on the response to exercise

ABBREVIATIONS: CPET=cardiopulmonary exercise testing; VO_{2max}=maximal oxygen uptake; VO_{2peak}=peak oxygen uptake.
NOTE: adapted from Bongers *et al*. [21]

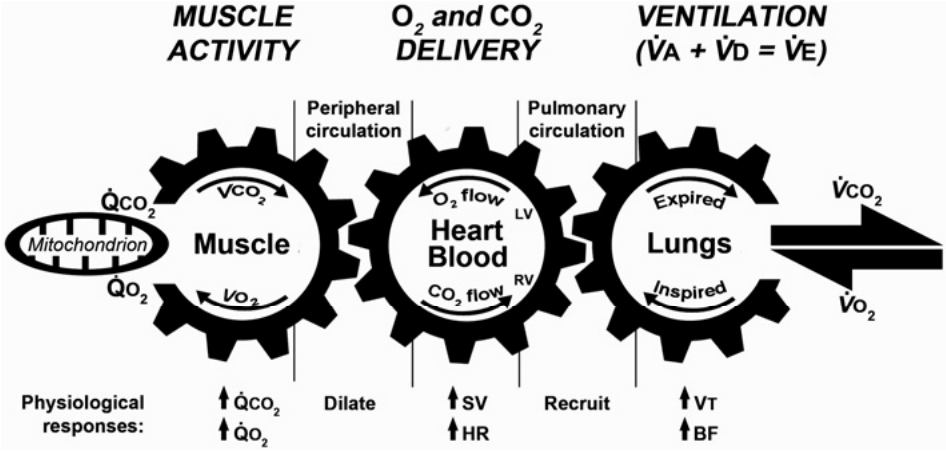

FIGURE 2. The integrative physiological response of the different organ systems to exercise.

ABBREVIATIONS: CO_2=carbon dioxide; BF=breathing frequency; HR=heart rate; LV=left ventricle; O_2=oxygen; QCO_2=carbon dioxide production by the exercising muscles; QO_2=oxygen uptake by the exercising muscles; RV=right ventricle; SV=left ventricular stroke volume; VT=tidal volume; VA=alveolar ventilation; VCO_2=carbon dioxide production; VD=physiological dead space; VE=minute ventilation; VO_2=oxygen uptake.
NOTE: adapted from Wasserman *et al*.[34]

Limitations of maximal cardiopulmonary exercise testing

As mentioned before, progressive CPET up to maximal exertion facilitates an accurate and objective assessment of the integrative physiological response to exercise of the pulmonary, cardiovascular, hematopoietic, and metabolic systems by measuring VO_{2max}. Throughout progressive CPET, oxygen uptake (VO_2) increases linearly with exercise intensity up to a point at which there is no further increase in VO_2, despite increasing exercise intensity.[35] Already in the 1920's, the classical studies of Nobel laureate Hill and his colleagues[36-39] demonstrated that an upper limit of the body's ability to deliver oxygen to the exercising muscles during progressive exercise exists.[40,41] The appearance of a clear plateau (asymptote) in VO_2 during progressive CPET, despite increasing exercise intensity, has conventionally been considered the best evidence for reaching and determining VO_{2max}.[22,42-44] Moreover, it provides the best indication of a maximal effort delivered by the participant. Additional 'objective' physiological criteria for a maximal effort during pediatric CPET are the attained HR, and the achieved respiratory exchange ratio (RER) at VO_{2max}. More specifically, it is recommended to use an HR at VO_{2max} of at least ≥95% of 195 beats·min^{-1} and an RER at VO_{2max} of at least ≥1.00 as supplementary criteria for a maximal effort during CPET on a cycle ergometer in pediatric

populations.[35] However, it is not uncommon that participants fail to attain a true plateau in $V\dot{O}_2$ during CPET,[30,45,46] especially in pediatric populations.[47,48] Therefore, the $V\dot{O}_2$ at peak exercise ($V\dot{O}_{2peak}$) is often used as a substitute for $V\dot{O}_{2max}$.[49] However, the attained $V\dot{O}_{2peak}$ is normally only considered valid when a child is able to attain the aforementioned supplementary criteria for a maximal effort at $V\dot{O}_{2peak}$. Moreover, it still remains unclear whether the child has really performed a maximal effort when meeting these criteria. Both $V\dot{O}_{2max}$ and $V\dot{O}_{2peak}$ are strongly influenced by the participant's motivation, the selected exercise protocol, verbal encouragement, and the skills and experience of the tester to determine peak exercise.[50-53] Most of these limitations are particularly important to consider in pediatric patient populations. In addition, performing CPET up to maximal exertion is not feasible in children or adolescents where maximal exercise testing is contraindicated or when performance may be impaired by pain, shortness of breath, or by fatigue rather than exertion.[54] The constraints that coincide with performing progressive CPET up to maximal exertion encouraged experts in the field of (clinical) exercise physiology to develop indices that do not rely on a maximal effort, such as the oxygen uptake efficiency slope (OUES).

The oxygen uptake efficiency slope

In order to develop an objective and independent submaximal measure of aerobic exercise capacity, the OUES was introduced by Baba *et al*. in 1996.[55] The OUES can be calculated in addition to the measured $V\dot{O}_{2peak}$ using exercise data collected during progressive CPET, or might even act as an alternative for $V\dot{O}_{2peak}$. The OUES concept is based on the curvilinear relationship between the minute ventilation ($V\dot{E}$) and $V\dot{O}_2$ during progressive CPET. The logarithmic transformation of the $V\dot{E}$ results in a linear relationship between $V\dot{E}$ and $V\dot{O}_2$. The regression coefficient of the regression line describing this linear relationship represents the OUES, a dimensionless quantity. The following equation is used to calculate the OUES[55]:

$$V\dot{O}_2 = a \times \text{Log } V\dot{E} + b$$

where '$V\dot{O}_2$' represents the oxygen uptake ($mL \cdot min^{-1}$), the constant 'a' is the rate of increase in the $V\dot{O}_2$ in response to an increasing $V\dot{E}$, which is defined as the OUES, 'Log $V\dot{E}$' is the common logarithm of the $V\dot{E}$ ($L \cdot min^{-1}$), and the constant 'b' is the intercept. FIGURE 3, upper graph, represents the curvilinear relationship between $V\dot{E}$ and $V\dot{O}_2$ throughout CPET in a healthy 15-year-old girl. FIGURE 3, lower graph, shows the logarithmic transformation of the $V\dot{E}$ that makes the relationship

between V_E and V_{O_2} linear, thereby facilitating the calculation of the OUES using linear least squares regression. Since the OUES is mathematically determined by a set of respiratory gas analysis data acquired during CPET, it is free from inter-observer variability.[56-58] Furthermore, the OUES should be insensitive to the used metabolic cart and the selected exercise protocol, since it is calculated from a ratio.[57]

In essence, the OUES provides an estimation of the efficiency of the V_E with respect to the V_{O_2}. Higher OUES values indicate a more efficient V_{O_2}, whereas lower OUES values represent a higher amount of V_E required for any given V_{O_2}.[59,60] As with aerobic exercise capacity, or $V_{O_{2peak}}$, each of the systems involved in the pathway for oxygen from the atmosphere to reach the mitochondria, might be a physiological limiting factor for the OUES.[61] Consequently, the OUES incorporates pulmonary, cardiovascular, hematopoietic, and metabolic function throughout progressive exercise in a single measure. Of particular importance for the OUES are the ventilatory threshold (VT; the point where lactic acid, generated during anaerobic glycolysis, begins to accumulate), as well as the ventilatory dead space ventilation (V_D/V_T ratio),[55,58,62] since they significantly influence ventilatory efficiency.

Due to the linearity of the OUES throughout the last part of CPET, the OUES theoretically does not require a maximal effort and is reliable when calculated using submaximal exercise data. This is an essential characteristic when a participant is either unwilling or unable to complete CPET up to maximal exertion. However, studies in different pediatric populations have reported inconclusive results concerning the linearity of the OUES during the last part of CPET. Similar submaximal and maximal OUES values were found in healthy children[63] and in obese children.[64] In contrast, two other studies found that the submaximal OUES was slightly, but significantly, lower than the maximal OUES in a combined group of healthy children and children with various heart diseases,[55] and in overweight children.[65]

Only two studies in healthy adults investigated the reliability of the OUES.[66,67] Both studies demonstrated that the OUES is highly reliable. In the study of van Laethem *et al*.,[67] a high intraclass correlation coefficient (ICC) of 0.93 (P<0.001) was found, which was comparable to that of $V_{O_{2peak}}$ (ICC: 0.95; P<0.001). However, the authors also reported that ICC values turned out to be higher when more data points were used to calculate the OUES.[67] This highlights the importance to continue exercising as long as possible towards peak exercise during CPET, in order to gain as many data points for the calculation of the OUES.

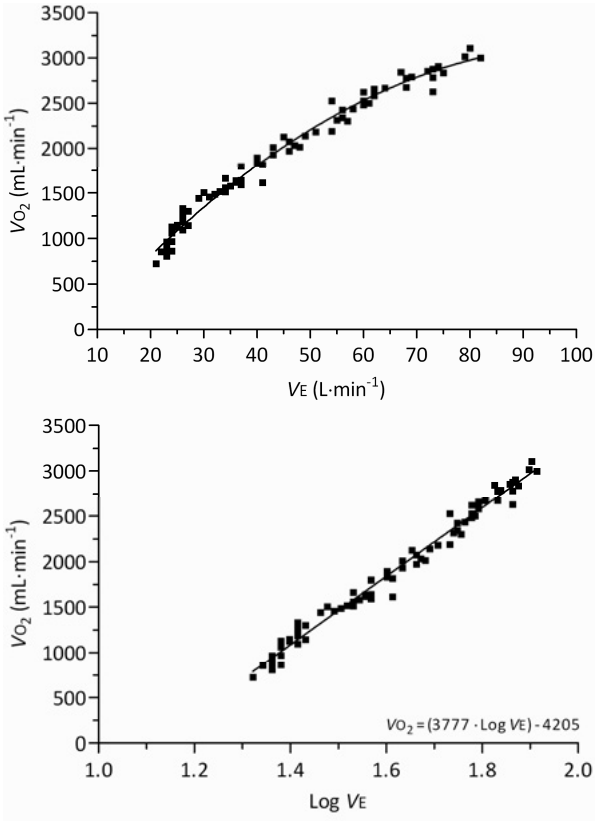

FIGURE 3. Relationship between the V_{O_2} and the V_E during CPET in a healthy 15-year-old girl. Data are presented as linear (upper graph) and semilog plots of the x-axis (lower graph), and the value of the OUES equals 3,777.

ABBREVIATIONS: CPET=cardiopulmonary exercise testing; Log V_E=common logarithm of the minute ventilation; OUES=oxygen uptake efficiency slope; V_E=minute ventilation; V_{O_2}=oxygen uptake.

The OUES has been reported to be highly correlated with $V_{O_{2peak}}$ in healthy children (r=0.922; P<0.001),[63] in obese children (r=0.906 and r=0.910; with P<0.001 for both coefficients),[64,68] and in a combined group consisting of healthy children and children with various heart diseases (r=0.941; P<0.001).[55] A study in overweight and obese children reported a slightly lower correlation coefficient between the OUES and $V_{O_{2peak}}$ (r=0.755; P<0.001).[65] These high correlation coefficients indicate that the OUES is a measure of aerobic exercise capacity.

In conclusion, the OUES might be a reliable and valid measure of aerobic exercise capacity in children and adolescents that does not require a maximal effort. The OUES is determinable in all participants[56,69] and could therefore be a valid measure of aerobic exercise capacity derived from submaximal exercise data in children that are unwilling or unable to perform a maximal effort. However, before the OUES can be implemented in daily pediatric (clinical) practice, more profound investigation concerning its validity is necessary in healthy children, as well as in pediatric patient populations.

Noncardiopulmonary exercise testing

Although the OUES might be a valid alternative to overcome the difficulty of assessing aerobic exercise capacity in children that are unable or unwilling to perform CPET up to maximal exertion, it still requires respiratory gas analysis measurements. Particularly in extramural care, performing respiratory gas analysis measurements throughout CPET is sometimes not feasible due to the expense, the need for special equipment, and the required trained staff.[70-72] Moreover, the use of a facemask or mouthpiece might frighten children.[73] Due to these limitations, standardized CPET remains underused in daily (clinical) practice,[74-76] despite its well-known clinical value. This underlines the need for non-sophisticated pediatric exercise testing procedures that do not require respiratory gas analysis measurements. A non-sophisticated, inexpensive, reliable, and valid alternative exercise test might help to increase the utilization of pediatric exercise testing.

The steep ramp test

The steep ramp test (SRT) is a noncardiopulmonary exercise test, since it does not require respiratory gas analysis measurements. The SRT is performed on a cycle ergometer and the attained peak WR (WR_{peak}) represents its primary outcome measure. Originally, the SRT was used to determine and optimize interval exercise training intensity in adult patients with chronic heart failure.[77,78] As described in these studies, the SRT protocol consists of three minutes of unloaded cycling, where after the WR is increased by 25 W·10 s^{-1} up to maximal exertion. Peak exercise is defined as the point at which there is a sustained drop in pedaling frequency from 60 revolutions·min^{-1}. The attained WR_{peak} at the SRT is termed 'maximal short-time exercise capacity' (MSEC). Compared to the Godfrey protocol for progressive pediatric CPET, the WR increases six times faster during the SRT protocol

(see FIGURE 4). Due to these fast WR increments, the attained WR_{peak} at the SRT largely exceeds the WR_{peak} achieved during regular CPET.[78-81] As a consequence of the rapid increase in WR, the test duration of the SRT is significantly shorter compared to CPET.

Despite significantly higher WR_{peak} values, the SRT does not seem to be physically more demanding than performing regular CPET. HR and blood pressure values, both measures of cardiac strain, were relatively low for the attained WR_{peak} values throughout the SRT compared to CPET values in adult patients with severe chronic heart failure.[78] A recent study in children with cystic fibrosis (CF) reported significantly higher values for the attained WR_{peak} at the SRT compared to CPET, whereas no significant differences were found for the HR at peak exercise ($HR_{peak)}$ and peak minute ventilation ($\dot{V}E_{peak}$).[81] Moreover, a study in adult patients with chronic obstructive pulmonary disease recently reported no significant differences in the metabolic and ventilatory response between the SRT and CPET, despite significantly higher WR_{peak} values reached at the SRT.[80] The SRT also seems to rely more on anaerobic glycolysis than CPET. Significantly higher values for blood lactate concentration were reported during the recovery phase of the SRT.[78] This suggests that anaerobic metabolism (adenosine triphosphate - phosphocreatine energy system and anaerobic glycolysis), rather than oxidative metabolism (aerobic energy system), is of greater importance during the SRT. This is confirmed by the finding that the $\dot{V}O_2$ for comparable WR values seems to be reduced during the SRT compared to CPET, which can be explained by a larger portion of anaerobic glycolysis in energy supply.[81] Thus, the SRT seems to provide intense exercise stimuli on the peripheral muscles, while not inducing additional cardiopulmonary strain.

Using a test-retest design, the SRT was reported to be a highly reliable exercise test in adult cancer survivors, since a high ICC for WR_{peak} was reported (0.996; $P<0.001$).[79] This was confirmed by a study in adult patients with chronic obstructive pulmonary disease (ICC: 0.990; $P<0.001$).[80] Moreover, a strong correlation was found between the attained WR_{peak} at the SRT and the $\dot{V}O_{2peak}$ achieved during regular CPET in adult cancer survivors (r=0.850; $P<0.001$).[79] This latter finding indicates that the SRT might be a valid test to provide an estimation concerning a participant's aerobic exercise capacity. Additionally, the SRT might even be used to monitor the effects of an exercise training intervention.

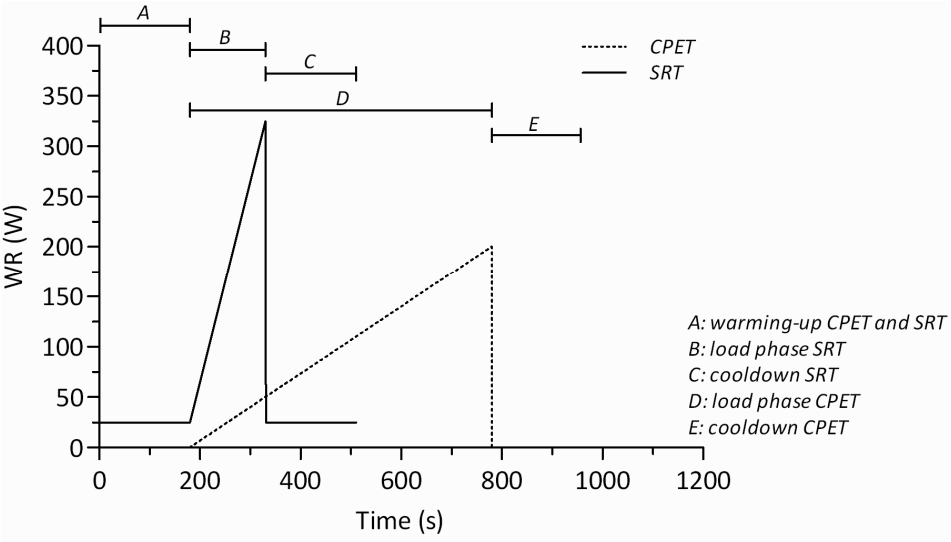

FIGURE 4. WR profile of CPET, according to the ramp version of the Godfrey protocol (20 W·min^{-1}), and the WR profile of the ramp version of the SRT protocol (20 W·10 s^{-1}).

ABBREVIATIONS: CPET=cardiopulmonary exercise testing; SRT=steep ramp test; WR=work rate.

In conclusion, noncardiopulmonary exercise testing with the attained WR_{peak} as primary outcome measure is a much less demanding procedure than CPET.[70] WR_{peak} has been found to be an appropriate alternative measure of $\dot{V}O_{2peak}$ in healthy children,[70] as well as in children with juvenile idiopathic arthritis.[72] The usefulness of the SRT in pediatric populations has not yet been investigated. Nevertheless, the SRT seems to be a feasible and reliable short-time incremental exercise test up to maximal exertion, in which the achieved WR_{peak} is its main outcome measure. Since the SRT does not require respiratory gas analysis measurements, it might help to increase the utilization of exercise testing in daily (clinical) practice. An additional advantage of the SRT is the strong association between the attained WR_{peak} at the SRT, and the $\dot{V}O_{2peak}$ obtained from traditional CPET. Therefore, the SRT might be useful as a simple screening tool that provides the clinician with an indication about a child's aerobic exercise capacity. However, prior to implementing the SRT in daily pediatric (clinical) practice, knowledge is required concerning its reliability and validity in healthy children, as well as in pediatric patient populations. Moreover, the physiological response to the SRT and CPET should be compared to each other in healthy children and in pediatric patient populations. In order to make the SRT suitable for pediatric populations, a modified SRT protocol should be used. The SRT protocol for children in the current

thesis therefore includes WR increments of 10, 15, or 20 W·10 s^{-1}, based on the child's body height, such as used in the Godfrey protocol[82] for pediatric CPET (<125 cm, 125 cm to 150 cm, and >150 cm, respectively). Since an accurate determination of the attained WR_{peak} is especially important during the SRT, a ramp version of the SRT protocol is highly recommendable. During the ramp version of the SRT in pediatric populations, the WR is recommended to be increased by 2, 3, or 4 W·2 s^{-1}, depending on the child's body height (see TABLE 2).

TABLE 2. WR profile of the ramp version of the SRT protocol in children.

	Body height		
	<125 cm	125 to 150 cm	>150 cm
WR during three-minute warming-up	25	25	25
WR increments (W·2 s^{-1})	2	3	4

ABBREVIATIONS: SRT=steep ramp test; WR=work rate.

Aims and outline of this thesis

Based on the previously described rationale, this thesis consists of two parts. The first part covers studies investigating the validity of the OUES as an exercise intensity independent measure of aerobic exercise capacity. The OUES can be calculated in addition to the measured $V\dot{O}_{2peak}$, or might even act as an alternative for $V\dot{O}_{2peak}$ when a submaximal effort is performed by the participant during progressive CPET. Since the constraints that coincide with performing progressive CPET up to maximal exertion are particularly considerable in pediatric patients with cardiopulmonary disease, this part comprises a study in healthy children, *CHAPTER 2*, as well as two studies, described in *CHAPTER 3* and *CHAPTER 4*, in two different pediatric patient populations with cardiopulmonary disease.

Specific aims of the first part of this thesis are:

- to investigate the characteristics and the validity of the OUES in a healthy pediatric population;
- to examine the characteristics and the validity of the OUES in children with congenital heart disease and in children with CF.

The second part of this thesis focuses on the applicability of the SRT as a non-sophisticated pediatric exercise test, which gives an indication concerning a child's aerobic exercise capacity, with no respiratory gas analysis measurements. The SRT

might be used for health screening in children and adolescents by evaluating aerobic exercise capacity. Therefore, the test characteristics of the SRT in healthy children and adolescents are described in *CHAPTER 5*, whereas pediatric norm values for SRT performance are presented in *CHAPTER 6*. To evaluate the usefulness of the SRT for daily clinical practice, the characteristics of the SRT in a pediatric clinical population suffering from CF are addressed in *CHAPTER 7*.

Specific aims of the second part of this thesis are:

- to examine the reliability and validity of the SRT in healthy children and adolescents, as well as to evaluate the physiological response to the SRT and CPET in healthy children and adolescents;
- to provide sex- and age-related norm values for SRT performance between the ages of 8 and 19 years;
- to evaluate SRT performance in a pediatric patient population, specifically in children and adolescents with CF, as well as to compare the physiological response to the SRT and CPET with each other in this population.

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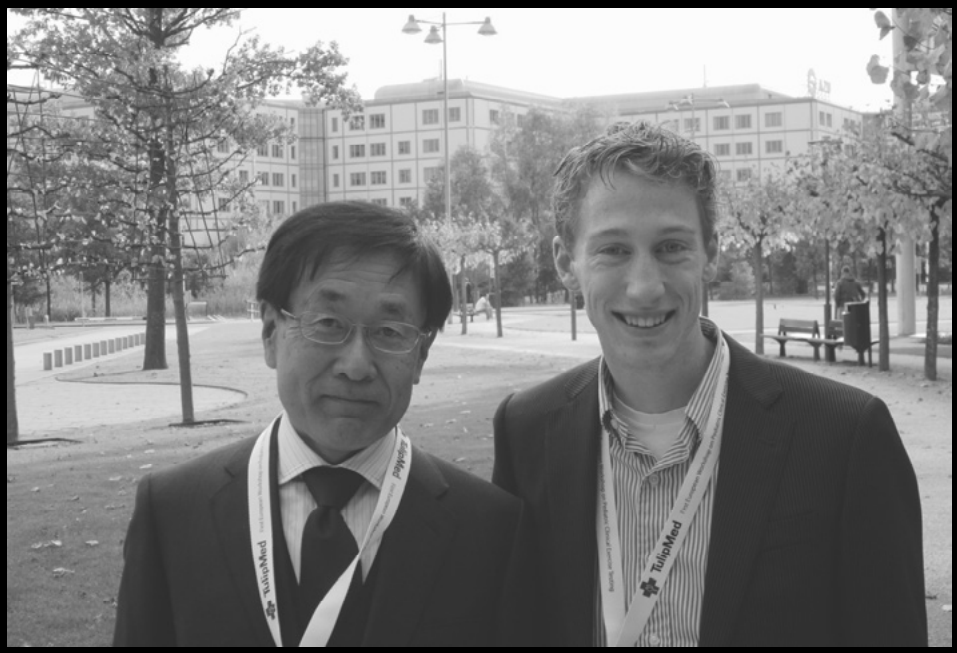
Part 1

The oxygen uptake efficiency slope



Dr. Reizo Baba, developer of the oxygen uptake efficiency slope and cardiologist at the Department of Cardiology, Aichi Children's Health and Medical Center, Obu city, Aichi, Japan, attending the First European Workshop for Pediatric Clinical Exercise Testing, October 19th – 20th, 2012, Utrecht, the Netherlands.

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Pediatric Exercise Science
2010;22:431-41

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Oxygen uptake efficiency slope in healthy children

Abstract

Background

Since the oxygen uptake efficiency slope (OUES) has originally been introduced as a submaximal measure of cardiopulmonary function, the objective of the current study was to investigate the characteristics of the submaximal OUES in a healthy pediatric population.

Methods

Cycle ergometry exercise tests with respiratory gas analysis were performed in 46 healthy children aged 7 to 17 years (27 boys, mean ± standard deviation [SD] age: 11.8 ± 2.2 years, and 19 girls, mean ± SD age: 12.9 ± 2.6 years). Maximal OUES, submaximal OUES, peak oxygen uptake (VO_{2peak}), peak minute ventilation (VE_{peak}), and the ventilatory threshold (VT) were determined.

Results

The submaximal OUES did not differ significantly from the maximal OUES (2201 ± 694 versus 2207 ± 704; P=0.296), even when the OUES values were expressed relative to body mass (P=0.413), body surface area (BSA) (P=0.370), and fat free mass (FFM) (P=0.579). The submaximal OUES correlated highly with VO_{2peak} (r=0.88; P<0.01), VE_{peak} (r=0.73; P<0.01), and the VT (r=0.85; P<0.01). Strong correlations were found with basic anthropometric variables (r values ranging from 0.53 to 0.84; with P<0.01 for all coefficients).

Conclusion

The submaximal OUES could provide an objective, independent measure of cardiopulmonary function in children, reflecting efficiency of ventilation. It is recommended to express OUES values relative to BSA or FFM in order to reduce the large inter-individual differences in OUES values.

Introduction

Cardiopulmonary exercise testing (CPET) is currently widely used in daily (clinical) practice to assess the response to exercise in both patients and in healthy individuals. Maximal oxygen uptake ($V\dot{O}_{2max}$), the highest rate at which an individual can consume oxygen during exercise, is widely recognized as the single best measure of a person's aerobic exercise capacity.[1] $V\dot{O}_{2max}$ requires maximal effort and leveling-off (plateau) of oxygen uptake, despite continuing exercise and increasing workload. Therefore, its application is mainly limited to healthy adults who can fulfill these requirements.[2] In pediatric populations, a true plateau in oxygen uptake is seldom attained.[3,4] Since several authors[4-6] have shown that a true plateau is not essential for defining the highest oxygen uptake in children, it gradually became more common to use the rate of oxygen uptake occurring at peak exercise ($V\dot{O}_{2peak}$).[2,7] However, the measurement of these parameters can be strongly influenced by the patients' motivation, the selected exercise protocol, and the experience of the tester.[2,8-10] Furthermore, exhaustive incremental tests for determining $V\dot{O}_{2peak}$ in pediatric populations generally do not mimic activity levels of their daily life. Therefore, exercise performance during submaximal exercise might be more representative in pediatric populations, especially in children with a chronic condition.

Baba *et al*.[11] introduced the oxygen uptake efficiency slope (OUES) in an attempt to develop an objective and effort-independent submaximal measure of cardiopulmonary reserve. Their approach involves deriving the regression coefficient of the semilog plot of minute ventilation (V_E) versus oxygen uptake ($V\dot{O}_2$). As such, the OUES provides an estimation of the efficiency of ventilation with respect to $V\dot{O}_2$, with steeper slopes indicating a greater ventilatory efficiency. Physiologically, the OUES is based on the development of metabolic acidosis, which is controlled by the distribution of blood to the skeletal muscles, as well as the physiological dead space, which is affected by the perfusion to the lungs.[9,11] The OUES was initially applied in a cohort of healthy children and children with heart disease.[9] However, the OUES has also been frequently investigated in healthy adults, adolescents, and patient populations.[12] To the authors' knowledge, merely five studies[3,11,13-15] examined the properties of the OUES in children and adolescents. All the aforementioned studies included healthy and/or overweight children, while the study of Baba *et al*.[11] also included children with heart disease.

To verify the assumption that the OUES is independent of exercise duration (effort), both maximal and submaximal values of OUES were calculated in four of

these studies.[3,11,14,15] Two studies[11,14] described that the submaximal OUES was slightly, however significantly, lower compared to the maximal OUES. One study[3] described higher submaximal OUES values, whereas a fourth study[15] did not describe any effects of exercise duration on the OUES. The OUES appears to be significantly higher in boys compared to girls (2335 ± 875 versus 1730 ± 580; and 2254 ± 735 versus 1943 ± 497)[3,15] and correlates significantly with basic anthropometric parameters, including age (r=0.83, r=0.76), body height (r=0.88, r=0.84), body mass (r=0.78, r=0.85), body mass index (BMI; r=0.48, r=0.57), body surface area (BSA; r=0.86), and fat free mass (FFM; r=0.86, r=0.84); with P<0.001 for all coefficients.[3,15] However, these characteristics were only examined for the maximal OUES and not for the submaximal OUES. In general, strong correlations were reported between the maximal OUES and $V\text{O}_{2\text{max}}$ (r=0.94; P<0.001) and $V\text{O}_{2\text{peak}}$ (r=0.77, r=0.91, r=0.92; with P<0.001 for all coefficients).[3,14,15] Only two studies[11,14] also assessed the aforementioned correlations for the submaximal OUES and reported a correlation with $V\text{O}_{2\text{max}}$ of r=0.95 (P<0.001) in healthy children and children with heart disease, and r=0.59 (P<0.001) in overweight adolescents, respectively.

Since the original rationale of the OUES was to provide a submaximal measure of cardiopulmonary function, which could be used as a possible substitute for, or in addition to, $V\text{O}_{2\text{peak}}$ or $V\text{O}_{2\text{max}}$ in populations unable to perform maximal exercise, it would be appropriate to examine submaximal OUES characteristics. Therefore, the aim of the current study was to investigate the properties of the submaximal OUES in a healthy pediatric population.

Methods

Participants

Forty-six children and adolescents (27 boys and 19 girls, aged 7 to 17 years) participated in this study. These participants included family members of the hospital staff as well as children living in the neighborhood of the hospital. All children were in good health, without chronic diseases, and were not on medication that might affect exercise capacity. Informed consent was obtained from the parents and/or from the children themselves if they were ≥12 years of age. The study protocol was approved by the Medical Ethics Committee of the University Medical Center Utrecht, the Netherlands.

Anthropometry

The participants' body mass (kg) and body height (m) were determined using an electronic scale (Seca 203; Seca, Hamburg, Germany) and a stadiometer (Ulmer Stadiometer; Prof. E. Heinze, Ulm, Germany) respectively. BMI ($kg \cdot m^{-2}$) was calculated using the following formula:

$$\text{BMI} = \frac{\text{body mass}}{\text{body height}^2}$$

in which 'BMI' represents the body mass index in $kg \cdot m^{-2}$ and 'body mass' and 'body height' are expressed in kg and m respectively. BSA was calculated using the equation of Haycock *et al*.[16]:

$$\text{BSA} = 0.024265 \times \text{body height}^{0.3964} \times \text{body mass}^{0.5378}$$

in which 'BSA' stands for body surface area in m^2, 'body height' is expressed in cm, and 'body mass' is expressed in kg. This equation is validated in infants, children, and adults.[16] Subcutaneous fat distribution was measured from skin fold thickness (mm) using a Harpenden skin fold caliper. The measurements were taken at four sites (at the right side of the body): triceps, biceps, subscapular, and supra-iliacal, according to Deurenberg *et al*.[17] The sum of the four skin folds ($\sum$4SF) was used to estimate the body density by means of the equations introduced by Deurenberg *et al*.[17] derived from anthropometric data of Dutch children aged 7 to 20 years. Body fat percentage (BF%) and subsequent FFM were estimated using a modification of the Siri equation proposed by Weststrate and Deurenberg.[18]

Cardiopulmonary exercise testing

CPET was performed using an electronically braked cycle ergometer (Lode Corival; Lode BV, Groningen, the Netherlands). The test started with one minute of unloaded cycling before the application of resistance to the ergometer. Subsequently, the work rate was increased by a constant increment of 10, 15, or 20 W every minute, according to the Godfrey protocol.[19] This protocol continued until the patient stopped because of maximal exertion, despite strong verbal encouragement of the test leader. Heart rate (HR) was measured continuously during CPET by using a three-lead electrocardiogram (Hewlett-Packard, Amstelveen, the Netherlands).

Analysis of expired gas

During CPET, participants breathed through a facemask (Hans Rudolph Inc, Kansas City, MO, USA), which was connected to a calibrated respiratory gas analysis system (Jaeger Oxycon Champion; Cardinal Health, Houten, the Netherlands). Expired gas passed through a flow meter (Triple V volume transducer), oxygen analyzer, and a carbon dioxide analyzer. The flow meter and gas analyzers were connected to a computer, which calculated breath-by-breath V_E, V_{O_2}, carbon dioxide output (V_{CO_2}), and the respiratory exchange ratio (RER) from conventional equations. Output from the gas analyzers was averaged at ten-second intervals and stored in a Microsoft Excel file for the off-line calculation of the OUES. A maximal effort was performed when at least one of the following criteria was met: an HR at peak exercise (HR_{peak}) >180 beats·min^{-1} or an RER at peak exercise (RER_{peak}) >1.0. $V_{O_{2peak}}$ and peak ventilation ($V_{E_{peak}}$) were determined as the average V_{O_2} and V_E values over the last 30 seconds during the maximal exercise test. The ventilatory threshold (VT) was determined as the level of V_{O_2} at which the linear relationship between V_{CO_2} and V_{O_2} disappeared, according to the V-slope method. The OUES was determined by plotting the V_{O_2} (mL·min^{-1}) against the common logarithm of the V_E (L·min^{-1}), and by calculating the regression coefficient of this linear relationship through single regression analysis (see *CHAPTER 1*).[11] For submaximal OUES determination, only data up to VT were included in the analyses. Data from the first minute of exercise were excluded because of the often very irregular breathing pattern at the onset of exercise.[20] Relative values for the exercise parameters were calculated by dividing the absolute values by body mass, FFM or BSA. Two studies reported good reliability of the OUES in healthy participants.[7,21]

Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS version 15.0; SPSS Inc., Chicago, IL, USA). Data are presented as mean values ± standard deviation (SD), and corresponding ranges. Differences between boys and girls were examined using the independent samples T-test for the anthropometric variables and the Mann-Whitney U test for the exercise parameters. A Wilcoxon signed-rank test was used to determine whether the submaximal OUES differed significantly from the maximal OUES. Spearman correlation coefficients were calculated to examine the relationship between the different exercise parameters and between the submaximal OUES and basic anthropometric variables. Significance was set a priori at the 0.05 level.

TABLE 3. Participant characteristics.

	Boys *(n=27)*		**Girls** *(n=19)*		
Age (years)	11.8 ± 2.2	[7.9 – 16.8]	12.9 ± 2.6	[8.4 – 16.5]	
Body height (m)	1.54 ± 0.15	[1.29 – 1.91]	1.59 ± 0.12	[1.39 – 1.79]	
Body mass (kg)	41.5 ± 12.0	[24.1 – 66.5]	49.4 ± 14.3	[28.2 – 81.7]	*
BMI ($kg \cdot m^{-2}$)	17.0 ± 2.0	[13.8 – 21.3]	19.0 ± 3.0	[14.6 – 25.5]	**
BSA (m^2) [a]	1.32 ± 0.25	[0.92 – 1.86]	1.47 ± 0.27	[1.03 – 2.02]	
∑4SF (mm)	28.9 ± 9.6	[19.7 – 65.2]	40.6 ± 14.3	[22.2 – 71.7]	**
Body density ($kg \cdot L^{-1}$) [b]	1.05 ± 0.01	[1.03 – 1.06]	1.04 ± 0.01	[1.03 – 1.06]	**
BF% (%) [c]	16.0 ± 3.2	[12.0 – 26.4]	20.9 ± 4.2	[14.4 – 28.7]	***
FFM (kg)	35.0 ± 10.1	[20.8 – 56.3]	38.8 ± 10.2	[24.1 – 59.7]	

Data are presented as mean ± SD, [range].

ABBREVIATIONS: ∑4SF=sum of the four skin folds; BF%=body fat percentage; BMI=body mass index; BSA=body surface area; FFM=fat free mass; SD=standard deviation; [a]: calculated using the equation of Haycock *et al.*[16]; [b]: calculated using the equation of Deurenberg *et al.*[17]; [c]: calculated using the equation of Weststrate and Deurenberg[18]; *: $P<0.05$; **: $P<0.01$; ***: $P<0.001$.

Results

Participant characteristics are depicted in TABLE 3. No significant differences were found between boys and girls regarding age, body height, BSA, and FFM, whereas body mass, BMI, Σ4SF, body density, and BF% were significantly lower in boys compared to girls. All maximal cardiopulmonary exercise tests were completed without adverse effects, such as dizziness, fainting, or vomiting. Results are presented in TABLE 4. During the interpretation of the exercise tests, the VT could not be properly determined in one participant. The average submaximal OUES of the entire population was 2200.5 ± 693.6, with values varying over a wide range (1062.6 to 4120.5; see FIGURE 5). After adjusting for the anthropometric variables body height (1383.8 ± 342.9; range: 764.5 to 2527.9), body mass (49.5 ± 9.9; range: 34.4 to 82.7), BMI (122.1 ±30.2; range 66.4 to 219.8), FFM (60.6 ± 10.7; range 39.7 to 97.0), and BSA (1569.9 ± 306.7; range 974.9 to 2747.0), the variation within submaximal OUES values was reduced.

TABLE 4. CPET results.

	Boys *(n=27)*		**Girls** *(n=19)*		
HR_{peak} (beats·min^{-1})	193 ± 8	[181 – 206]	194 ± 7	[180 – 212]	
RER_{peak}	1.15 ± 0.06	[1.02 – 1.28]	1.16 ± 0.08	[1.01 – 1.29]	
VT (mL·min^{-1}) [a]	1534 ± 468	[830 – 2712]	1425 ± 499	[936 – 2767]	
VO_{2peak} (mL·min^{-1})	2188 ± 671	[1150 – 3590]	2177 ± 808	[1230 – 4140]	
VO_{2peak}/kg (mL·kg^{-1}·min^{-1})	52.9 ± 6.7	[40.3 – 63.3]	43.6 ± 5.5	[33.6 – 55.6]	***
VO_{2peak}/BSA (mL·m^{-2}·min^{-1})	1633 ± 248	[1129 – 2087]	1449 ± 276	[1139 – 2103]	*
VO_{2peak}/FFM (mL·kg^{-1}·min^{-1})	62.9 ± 7.3	[49.4 – 74.5]	55.8± 6.8	[46.7 – 71.3]	**
VE_{peak} (L·min^{-1})	77.7 ± 25.1	[45.2 – 149.5]	76.1 ± 28.2	[44.6 – 144.3]	
VE_{peak}/kg (L·kg^{-1}·min^{-1})	1.88 ± 0.28	[1.42 – 2.40]	1.55 ± 0.32	[0.82 – 2.06]	**
VE_{peak}/BSA (L·m^{-2}·min^{-1})	58.1 ± 9.6	[41.7 – 80.4]	51.2 ± 11.8	[28.6 – 78.0]	*
VE_{peak}/FFM (L·kg^{-1}·min^{-1})	2.25 ± 0.29	[1.68 – 2.76]	1.96 ± 0.40	[1.15 – 2.64]	*
Maximal OUES	2185 ± 676	[849 – 3522]	2237 ± 760	[1236 – 3777]	
Maximal OUES/kg	52.9 ± 8.6	[35.2 – 70.7]	45.2 ± 6.1	[37.3 – 59.9]	**
Maximal OUES/BSA	1632 ± 294	[923 – 2348]	1496 ± 261	[1145 – 1999]	
Maximal OUES/FFM	62.7 ± 9.7	[40.9 – 82.8]	57.5 ± 7.1	[47.3 – 71.1]	*
Submaximal OUES [a]	2157 ± 669	[1063 – 4121]	2260 ± 741	[1405 – 4075]	
Submaximal OUES/kg [a]	51.8 ± 10.3	[34.4 – 82.7]	46.3 ± 8.5	[36.0 – 62.9]	
Submaximal OUES/BSA [a]	1603 ± 324	[975 – 2747]	1525 ± 284	[1202 – 2202]	
Submaximal OUES/FFM [a]	61.7 ± 11.8	[39.7 – 97.0]	59.2 ± 9.1	[46.2 – 74.7]	

Data are presented as mean ± SD, [range].

ABBREVIATIONS: BSA=body surface area; CPET=cardiopulmonary exercise testing; FFM=fat free mass; HR_{peak}=peak heart rate; OUES=oxygen uptake efficiency slope; RER_{peak}=peak respiratory exchange ratio; SD=standard deviation; VE_{peak}=peak minute ventilation; VO_{2peak}=peak oxygen uptake; VT=ventilatory threshold; [a]: VT was not determinable in 1 boy, so in this case *n*=26 for the boys; *: *P*<0.05; **: *P*<0.01; ***: *P*<0.001.

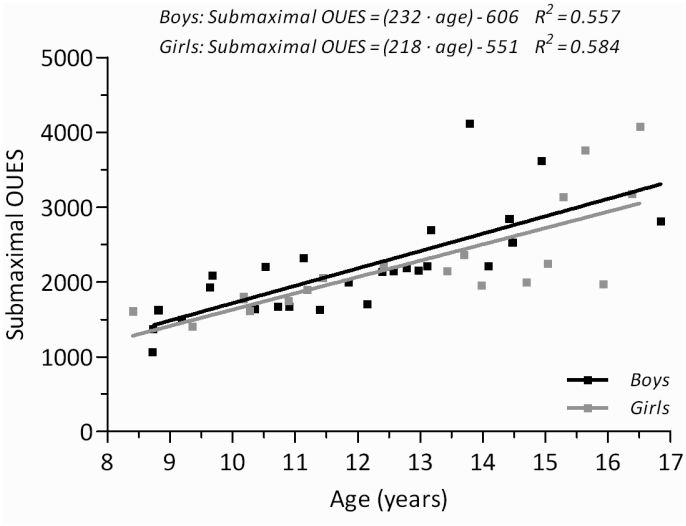

FIGURE 5. Age-related changes in submaximal OUES values.

ABBREVIATION: OUES=oxygen uptake efficiency slope.

The submaximal OUES did not differ significantly from the maximal OUES (P=0.296), even when the OUES values were expressed relative to body mass (P=0.413), BSA (P=0.370), and FFM (P=0.579). A Bland-Altman plot of the maximal OUES versus the submaximal OUES is shown in FIGURE 6. Furthermore, a strong correlation was observed between both parameters (r=0.92). The submaximal OUES showed a high correlation with $V\mathrm{O}_{2\mathrm{peak}}$ (r=0.88), $V\mathrm{E}_{\mathrm{peak}}$ (r=0.73), and VT (r=0.85); with P<0.01 for all coefficients. However, when normalized for body mass, the correlations with $V\mathrm{O}_{2\mathrm{peak}}$ and $V\mathrm{E}_{\mathrm{peak}}$ declined (r=0.60 and r=0.51, respectively; with P<0.01 for both coefficients). Similarly, lower correlations were found when normalized for BSA (r=0.67 and r=0.45, respectively) or FFM (r=0.49 and r=0.39, respectively); with P<0.01 for all coefficients. No significant sex differences were found for the absolute values of all studied exercise parameters (data not shown). However, when expressed relative to body mass, BSA or FFM, both $V\mathrm{O}_{2\mathrm{peak}}$ and $V\mathrm{E}_{\mathrm{peak}}$ were significantly higher in boys compared to girls, whereas adjustment of the submaximal OUES did not result in sex differences. High correlations were found between the submaximal OUES and basic anthropometric variables, including body height (r=0.82), BSA (r=0.77), age (r=0.82), body mass (r=0.75), FFM (r=0.84) and BMI (r=0.53); with P<0.01 for all coefficients. The submaximal OUES appeared to increase linearly with age, as is shown in FIGURE 5.

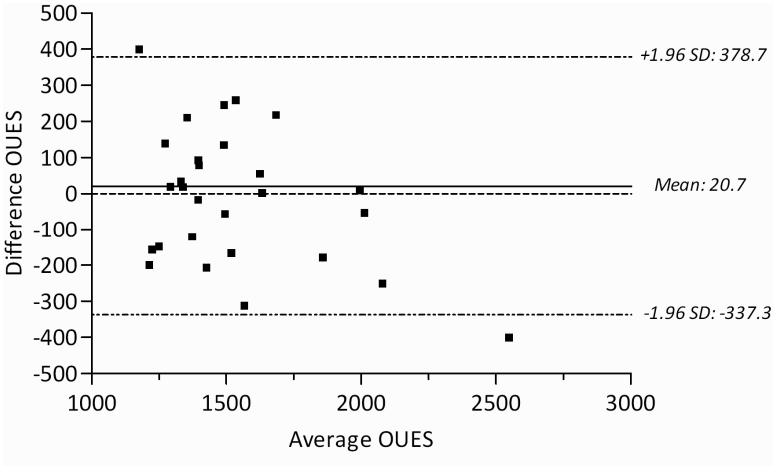

FIGURE 6. Bland-Altman plot of the maximal OUES/BSA and the submaximal OUES/BSA, showing the bias (difference in mean) and limits of agreement.

ABBREVIATIONS: BSA=body surface area; OUES=oxygen uptake efficiency slope; SD=standard deviation.

Discussion

This study describes submaximal OUES characteristics in a healthy pediatric population, aged 7 to 17 years. The main findings indicate that the OUES in healthy children is independent of exercise intensity, correlates highly with other exercise parameters (such as $V\text{O}_{2\text{peak}}$, $V\text{E}_{\text{peak}}$, VT), and shows a linear increase with age during childhood and adolescence. However, the results also illustrate that the OUES is considerably influenced by anthropometric variables and that its values show large inter-individual variation.

The submaximal OUES values found in the current population are in line with earlier studies of children with corresponding ages,[3,15] despite the fact that those two studies used a treadmill rather than a cycle ergometer to perform the maximal exercise tests. The strong correlation between the submaximal OUES and $V\text{O}_{2\text{peak}}$ also is in line with the results of Baba *et al.*,[11] who reported a very strong correlation between the submaximal OUES and $V\text{O}_{2\text{max}}$ (r=0.95; P<0.001). The submaximal OUES did not differ significantly from the maximal OUES in the current study, which confirms the results of Marinov *et al.*[15] Other studies, however, found submaximal OUES values to be slightly, but significantly, higher[3] or lower[11,14] compared to maximal OUES values. Large inter-individual differences in OUES values

might be responsible for these inconsistent findings among the abovementioned studies. Although previous studies reported the OUES to be significantly higher in boys compared to girls, the current study suggests that although boys generally achieve higher peak values in both V_{O_2} and V_E, their ventilatory efficiency (OUES) does not differ significantly from girls.

The strong correlations between the submaximal OUES and various basic anthropometric variables in this study reflect changes in ventilatory efficiency during childhood and adolescence, and are in line with values found for the maximal OUES in earlier studies.[3,15] During maturation, with the associated changes in body height, body mass, and body composition, absolute peak values of both V_E and V_{O_2} will also change, which makes it reasonable that this will affect the OUES as well. Maximal indices such as $V_{O_{2peak}}$ are known to be strongly influenced by changes in body size. Therefore, $V_{O_{2peak}}$ is often expressed in relation to body mass. However, this does not fully compensate the influence of body size on $V_{O_{2peak}}$.[22] The study of Marinov and Kostianev[3] showed that normalizing $V_{O_{2peak}}$ by dividing it by BSA compensates for the differences between various weight groups. Therefore, OUES during childhood should be interpreted with caution, which is in line with the current study results which indicate that the submaximal OUES in children is considerably influenced by anthropometric variables. Adjusting its values for body size seems appropriate, especially in children. Previous studies have expressed OUES values relative to body mass, FFM, and BSA. The current study results indicate that FFM will reduce the overall variability to the greatest extent, followed by BSA, and hence adjustment of submaximal OUES values for FFM or BSA in children seems recommendable. From a physiological perspective, FFM provides the best indication of $V_{O_{2peak}}$ (since a direct relationship is assumed between muscle mass and its capacity to consume oxygen for aerobic metabolism),[23-25] whereas BSA is supposed to provide a more precise indication of body volume compared to merely body height or body mass.[26,27]

The present study has some limitations, such as the relatively small and heterogeneous population, which could be responsible for the large inter-individual variation and skewed distributions. During data exploration five individuals were detected as outliers. All deviated on the top side of the box plot, indicating that they had a significantly higher aerobic exercise capacity than the rest of the group. Profound investigation revealed that these participants were significantly older than the other participants (15.45 ± 1.12 versus 11.83 ± 2.25 years respectively; $P<0.001$), participated regularly (>3 hours·week^{-1}) in endurance sports, and showed significantly higher $V_{O_{2peak}}$ values. As a result of their physical activity patterns, these participants may be more highly trained and therefore may not be

representative for an average pediatric population. Elimination of the outliers resulted in a decrease in overall distribution of OUES values. Nevertheless, this might be a first indication of the responsiveness of the OUES with exercise training in children.

Furthermore, appropriate cut-off values should be used for submaximal OUES determination. At present however, it remains unclear which endpoint approach is most useful to simulate submaximal effort (approaches based on RER, VT, heart rate reserve, or a percentage of exercise duration or $V\text{O}_{2\text{max}}$).[12] In the current study, VT was used as a cut-off value for submaximal OUES determination, although VT cannot always be determined and its values depend on the method used for detection.[28] Shimizu *et al*.[28] showed that the V-slope method had consistently good agreement among observers (with intra-class correlation coefficients ranging from 0.85 to 0.98), and was least affected by the used exercise protocol. Furthermore, the study of Wasserman[29] identified this method as the most practical method. Since the submaximal OUES is derived from multiple data points up to VT and the OUES appears to be effort-independent,[15,30-32] the exact endpoints will nonetheless not have influenced OUES values to a great extent.

There is a need for adequate reference values for the OUES in (healthy) children. Appropriate reference values should be generated with respect to age, sex, race, and other relevant factors such as maturation and anthropometrics. To the author's knowledge, influences of puberty on the OUES have not yet been investigated. Since puberty could lead to significant changes in body composition, muscle strength, $V\text{E}_{\text{peak}}$, the ventilatory equivalents, and physical activity patterns, it might also influence ventilatory efficiency (OUES). Future studies should address these variables. Moreover, it is currently unknown whether the submaximal OUES is able to differentiate between healthy children and children with a (chronic) disease. Previous findings suggest that the OUES has a discriminative value in adults,[2,9,32-34] however, further research is required to assess its discriminative properties in different pediatric populations. The responsiveness of the OUES to physical training is another issue that has not yet been addressed in pediatric populations. Results from studies in adults suggest that the OUES increases following physical training in cardiac patients.[35-37]

The OUES is useful to evaluate progression in exercise capacity, given that an increase in OUES values suggests that a similar $V\text{O}_2$ is achieved with lower ventilatory cost (increase in efficiency).[35-37] Several authors even state that the OUES is more stable and robust than the maximal parameter $V\text{O}_{2\text{peak}}$, since peak work rate attained during symptom-limited CPET can be influenced by multiple factors.[2,32,36]

However, large inter-individual variation may limit the usefulness of the OUES in daily (clinical) practice. To the best of the authors' knowledge, none of the studies in the current literature addressing the OUES investigated the practical application of the OUES by correlating OUES values in children with their running speeds or other practical test criteria. However, children with higher $V\mathrm{O}_{2\mathrm{peak}}$ values, indicating better endurance performance, show higher OUES values than children with lower values for $V\mathrm{O}_{2\mathrm{peak}}$. The responsiveness and the practical application of the OUES in pediatric populations remains subject of further research.

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European Journal of Cardiovascular Prevention and Rehabilitation
2011;18:384-92

The oxygen uptake efficiency slope in children with congenital heart disease

Construct and group validity

Abstract

Background

The oxygen uptake efficiency slope (OUES) has been introduced as an independent and objective alternative to the peak oxygen uptake (VO_{2peak}), which does not require maximal exercise. The aim of this study was to investigate the construct and group validity of the OUES in children with congenital heart disease (CHD).

Methods

Thirty-one patients with CHD, of which 16 patients (mean age ± standard deviation [SD] 11.2 ± 2.7 years) with a Fontan repair and 15 patients (13.2 ± 3.6 years) with surgical repair of tetralogy of Fallot (ToF), completed a symptom-limited cardiopulmonary exercise testing. The OUES was calculated and normalized for body surface area (OUES/BSA) at three different exercise intensities: (1) using 100% of the exercise data; (2) using the first 75% of the exercise data; and (3) using exercise data up to the ventilatory threshold (VT). Furthermore, VO_{2peak}, VT, the regression coefficient of the relationship between the minute ventilation and the oxygen uptake (VE/VO_2-slope), and the regression coefficient of the relationship between the minute ventilation and the carbon dioxide production (VE/VCO_2-slope) were calculated and compared to values of 46 healthy children (12.2 ± 2.4 years).

Results

In all three groups, the OUES/BSA values determined at the three different exercise intensities were not significantly different from each other. Moreover, the OUES/BSA was significantly reduced in the children with CHD (1237 ± 279 versus 1576 ± 186; $P<0.001$), with significantly lower values in the Fontan patients compared to ToF patients (1108 ± 234 versus 1374 ± 262; $P<0.001$). Moderate to strong correlations were found between the OUES/BSA and both the VO_{2peak} (r values ranging from 0.324, not significant, to 0.750; with $P<0.05$ for the other coefficients) and VT (r values ranging from 0.536 to 0.775; with $P<0.05$ for all coefficients) in both Fontan and ToF patients.

Conclusion

The OUES provides a valid measure of aerobic exercise capacity in children with CHD, which is independent of exercise intensity and strongly correlated to VO_{2peak} and VT (construct validity). Similar to VO_{2peak}, the OUES is capable of differentiating between healthy children and children with CHD, as well as between Fontan and ToF patients (group validity). Therefore, the OUES may be a valid, effort-independent parameter of aerobic exercise capacity in children with CHD.

Introduction

The importance of cardiopulmonary exercise testing (CPET) is becoming more accepted in daily (clinical) practice. The results of CPET can be used at all stages of clinical assessment (e.g. diagnosis and characterization of disease severity, progression, prognosis, and response to treatment).[1,2] In children with congenital heart disease (CHD), the main indication for CPET is the evaluation of aerobic exercise capacity.[3] Since cardiopulmonary function testing at rest cannot predict an individual's aerobic exercise capacity reliably,[4] the measurement of the maximal oxygen uptake ($V\mathrm{O}_{2\mathrm{max}}$) during CPET is currently the only modality that provides an accurate and objective indication of aerobic exercise capacity.

Classically, the $V\mathrm{O}_{2\mathrm{max}}$ describes a point at which there is no further increase in oxygen uptake ($V\mathrm{O}_2$), despite a further increase in exercise intensity.[5] Unfortunately, $V\mathrm{O}_{2\mathrm{max}}$ cannot be measured directly in individuals who are unable or unwilling to perform at maximal effort. Moreover, a true plateau in $V\mathrm{O}_2$ is seldom attained during CPET.[6–10] In practice however, the $V\mathrm{O}_{2\mathrm{max}}$ is interchangeable with the $V\mathrm{O}_2$ measured at peak exercise ($V\mathrm{O}_{2\mathrm{peak}}$).[11–13] Still, measuring the $V\mathrm{O}_{2\mathrm{peak}}$ is influenced by the motivation of the patient, the exercise protocol, and the skills and experience of the tester.[13–18]

To avoid the latter influences, Baba *et al.*[19] introduced the oxygen uptake efficiency slope (OUES) for children with CHD, which includes a submaximal parameter that might act as an alternative for the $V\mathrm{O}_{2\mathrm{peak}}$. The OUES describes the relationship between the $V\mathrm{O}_2$ and the common logarithm of the minute ventilation ($V\mathrm{E}$) throughout CPET, representing how efficiently oxygen is extracted by the lungs and used in the periphery. Similar to the regression coefficient of the relationship between the $V\mathrm{E}$ and the clearance of the carbon dioxide ($V\mathrm{CO}_2$) produced by metabolically active tissues ($V\mathrm{E}/V\mathrm{CO}_2$-slope), its linearity during the last part of CPET implies that the use of submaximal exercise data on or after the ventilatory threshold (VT) does not significantly alter the OUES results.[12,13,20–22]

The OUES has been extensively investigated in healthy adults and in adult patients within a wide range of heart conditions, including heart failure,[13,15,20,23–31] coronary artery disease,[32–35] and CHD.[36] However, only one study[19] addressed the OUES in children with various cardiac conditions. In this latter study, no distinction was made between healthy children and children with CHD. Thus, at present, the applicability of the OUES in pediatric patients with CHD is unknown.[37]

Therefore, the current study aims to investigate the construct validity and group validity of the OUES in children with CHD in order to assess its usefulness in these patients. Construct validity will be studied by using OUES values determined at different exercise intensities, as well as by using the associations between the OUES and other indices for aerobic exercise capacity (e.g. $V\text{O}_{2\text{peak}}$ and the VT). Group validity will be determined comparing the OUES data between children with CHD and healthy controls.

Methods

Participants

The study population consisted of 31 pediatric patients with CHD (with a mean age ± standard deviation [SD] of 12.1 ± 3.2 years, range 8.0 – 18.8 years) from the Wilhelmina Children's Hospital, University Medical Center Utrecht, who underwent CPET as part of their regular check-up. Within the CHD population of this study, 16 patients (11.2 ± 2.7 years of age, range 8.2 – 16.5 years) had a total cavopulmonary connection (Fontan circulation). Mean age ± SD at first surgery in these patients was 2.7 ± 6.5 months. After the Fontan procedure, 12 patients (75%) had a morphologically left systemic ventricle and four patients (25%) had a morpho-logically right systemic ventricle. The remaining 15 patients with CHD (13.0 ± 3.5 years of age, range 8.0 – 18.8 years) had undergone surgical repair for tetralogy of Fallot (ToF) at a mean age ± SD of 19.6 ± 29.6 months. Echocardiographic characteristics of the ToF patients are shown in TABLE 5. In addition, exercise data retrieved from 46 healthy children (12.2 ± 2.4 years of age, range 7.9 – 16.8 years) who underwent CPET in the authors' laboratory were used. The healthy participants were family members of the hospital staff and children living in the neighborhood of the hospital. No healthy control had cardiac, vascular, pulmonary, or musculoskeletal disease. Informed consent was obtained from the parents and, if older than 12 years of age, from the children as well. The research protocol was approved by the Medical Ethics Committee of the University Medical Center Utrecht, the Netherlands.

TABLE 5. Echocardiographic characteristics after corrective surgery in ToF patients.

Variable	ToF *(n=15)*
Initial corrective surgery:	
VSD patch	15 (100%)
Infundibulectomy	15 (100%)
Commissurotomy	4 (27%)
TAP	10 (67%)
No outflow tract patch	1 (7%)
Pulmonary regurgitation:	
Slight	2 (13%)
Mild	1 (7%)
Moderate	3 (20%)
Severe	9 (60%)
Right ventricle size:	
Normal	4 (27%)
Slightly enlarged	4 (27%)
Moderately enlarged	6 (40%)
Severely enlarged	1 (7%)
Right ventricle function:	
Normal/enhanced	14 (93%)
Slightly reduced	1 (7%)

Data are presented as n (%).
ABBREVIATIONS: TAP=transannular patch; ToF=tetralogy of Fallot; VSD=ventricular septal defect.

Anthropometry

Prior to CPET, anthropometric measurements were completed in all participants, including body mass (kg) and body height (m), using an electronic scale (Seca 203; Seca, Hamburg, Germany) and a stadiometer (Ulmer Stadiometer; Prof. E. Heinze, Ulm, Germany) respectively. Body mass index (BMI; $kg \cdot m^{-2}$) was calculated as the body mass divided by body height squared (see *CHAPTER 2*). SD scores were calculated for BMI for age, using Dutch growth charts.[38] For the estimation of the body surface area (BSA; m^2), the equation of Haycock *et al.*[39] was used, which is validated in infants, children, and adults (see *CHAPTER 2*).

Cardiopulmonary exercise testing

All patients underwent CPET using an electronically braked cycle ergometer (Lode Corival; Groningen, the Netherlands). After assessment of baseline cardiopulmonary values, the work rate was increased by a constant increment of 10, 15, or 20 $W \cdot min^{-1}$, depending on the estimated fitness level, to bring the patient to his or her limit between eight and twelve minutes of exercise. During CPET, patients had to maintain a pedaling rate between 60 and 80 $revolutions \cdot min^{-1}$. This protocol continued until the patient stopped because of maximal exertion, despite strong verbal encouragement of the investigators. Heart rate (HR) was monitored using a twelve-lead electrocardiogram (Hewlett-Packard, Amstelveen, the Netherlands), and the peripheral oxygen saturation (Sp_{O_2}) was measured at the index finger by pulse oximetry (Nellcor 200 E; Nellcor, Breda, the Netherlands). During CPET, participants breathed through a facemask (Hans Rudolph, Kansas City, MO, USA) connected to a calibrated respiratory gas analysis system (Jaeger Oxycon Pro; Care Fusion, Houten, the Netherlands). Expired gas was passed through a flow meter (Triple V volume transducer), an oxygen analyzer, and a carbon dioxide analyzer. The flow meter and gas analyzers were connected to a computer, which calculated breath-by-breath V_E, V_{O_2}, V_{CO_2}, and the respiratory exchange ratio (RER) averaged at ten-second intervals. Maximal effort was reached when participants showed clinical signs of intense effort, were unable to maintain the required pedaling rate, and when at least one of the following criteria was met: an HR at peak exercise (HR_{peak}) >180 $beats \cdot min^{-1}$ or an RER at peak exercise (RER_{peak}) >1.0. Absolute peak values were calculated as the average value over the last 30 seconds during CPET. The point at which a change in the linear relationship between the V_{CO_2} and V_{O_2} was detected, was defined as the VT, according to the V-slope method.[40] The regression coefficient of the relationship between the V_E and the V_{O_2} (V_E/V_{O_2}-slope) and the V_E/V_{CO_2}-slope were calculated by linear least squares regression. The OUES was calculated by linear least squares regression of the V_{O_2} on the common logarithm of the V_E, by using the equation introduced by Baba *et al.*[19] (see *CHAPTER 1*). A steeper slope, reflected by a higher OUES, represents a more efficient V_{O_2}: a smaller ventilation quantity is required for a certain V_{O_2} (see FIGURE 7). For the determination of the OUES 100, all data gained during CPET were included, whereas for the determination of the OUES 75, data up to 75% of the exercise duration were included in the analyses. The OUES VT was calculated by means of the collected exercise data up to the VT. Absolute exercise variables were expressed as relative values as well, by dividing the absolute values by body mass or BSA. Due to the variable anthropometric changes in children as a result of their growth, development, and maturation, the authors' research group recently recommended

normalizing OUES values relative to BSA (OUES/BSA) or fat free mass in children, since this reduced the variability between participants to the greatest extent.[41]

Statistical analysis

The Statistical Package for the Social Sciences (SPSS version 15.0; SPSS Inc., Chicago, USA) was used for data analyses. Data are presented as mean values ± SD. Shapiro-Wilk tests for normality were used to evaluate the distribution of the data. One-way analysis of variance (ANOVA) was performed on the anthropometric data to test for significant differences between the three groups. Kruskal-Wallis ANOVA was applied on the exercise data to test for significant differences between groups (group validity). Within group differences between the OUES values determined at different exercise intensities were evaluated with a Friedman test (construct validity). Additional post hoc comparisons were performed on the one-way ANOVA outcomes to identify the exact significant differences by using Fisher's least significant difference (LSD) tests. Mann-Whitney U tests with Holm's sequential Bonferroni adjustment were performed on the Kruswal-Wallis ANOVA outcomes to locate the exact significant differences between the groups. Receiver operator characteristic (ROC) curves analysis was used to identify the cut-off value of percentage of predicted OUES 75/BSA values between children with CHD and healthy controls. OUES 75/BSA values were predicted using the following formula:

$$\text{OUES 75/BSA} = 998.833 + (46.362 \times \text{age})$$

which was established in the current sample of healthy children. In this formula, 'OUES 75/BSA' represents the oxygen uptake efficiency slope, calculated using the first 75% of the exercise data and normalized for body surface area and 'age' is expressed in years. Spearman correlation coefficients were calculated to examine associations between exercise variables and the OUES (construct validity). A *P*-value <0.05 was considered statistically significant.

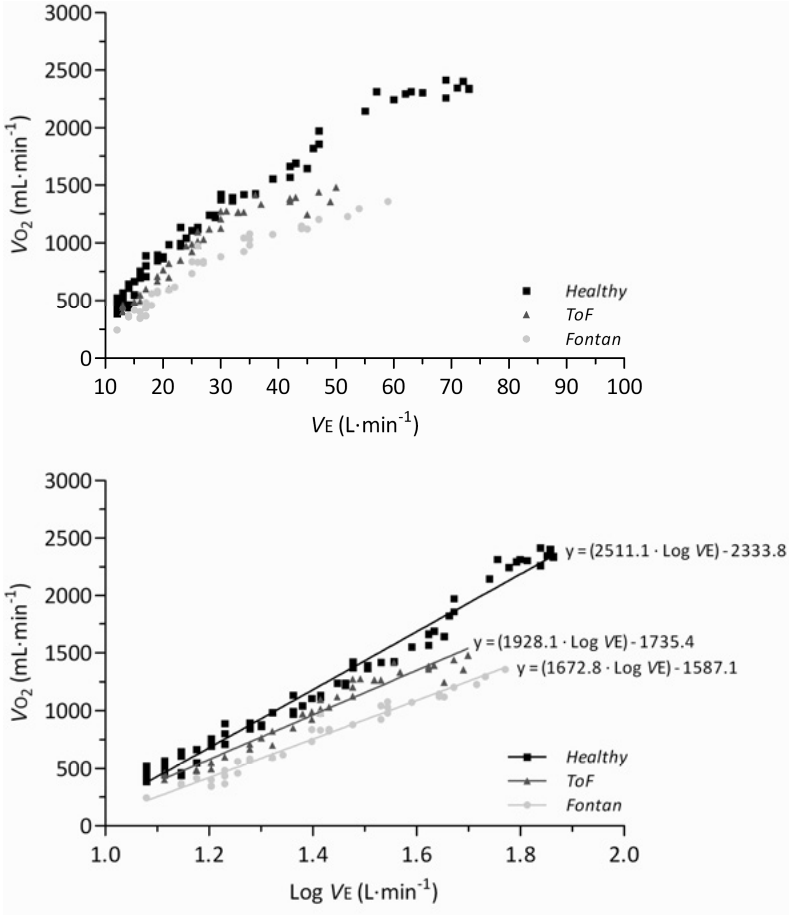

FIGURE 7. Relationship between the V_{O_2} and the V_E during CPET in a healthy 13-year-old boy, in a sex- and age-matched patient with ToF, and in a sex- and age-matched patient with a Fontan circulation. The values of the OUES are 2511.1, 1928.1, and 1672.8 respectively, and the data are presented as linear (upper graph) and semilog plots of the x-axis (lower graph).

ABBREVIATIONS: CPET=cardiopulmonary exercise testing; Log V_E=common logarithm of the minute ventilation; OUES=oxygen uptake efficiency slope; ToF=tetralogy of Fallot; V_E=minute ventilation; V_{O_2}=oxygen uptake.

TABLE 6. Participant characteristics.

	Healthy *(n=46)*	**ToF** *(n=15)*	***P****	**Fontan** *(n=16)*	***P*^#^**	***P*^†^**
Sex (male/female)	27/19	9/6		10/6		
Age at first surgery (months) [a]	NA	12.4 ± 7.8	*NA*	2.7 ± 6.5	*NA*	<0.001 ***
Age at CPET (years)	12.2 ± 2.4	13.2 ± 3.5	*NS*	11.2 ± 2.7	*NS*	0.049 *
Body height (m)	1.6 ± 0.1	1.6 ± 0.2	*NS*	1.4 ± 0.1	0.003 **	0.030 *
Body mass (kg)	44.7 ± 13.4	44.2 ± 14.5	*NS*	34.9 ± 6.4	0.009 **	0.042 *
BMI ($kg \cdot m^{-2}$)	17.9 ± 2.6	17.8 ± 3.0	*NS*	16.6 ± 2.1	*NS*	*NS*
BMI SD score [b]	-0.1 ± 0.9	-0.5 ± 1.2	*NS*	-0.5 ± 1.2	*NS*	*NS*
BSA (m^2) [c]	1.4 ± 0.3	1.4 ± 0.3	*NS*	1.2 ± 0.1	0.013	0.036 *

Data are presented as mean ± SD.

ABBREVIATIONS: BMI=body mass index; BSA=body surface area; CPET=cardiopulmonary exercise testing; NA=not applicable; NS=not significant; SD=standard deviation; ToF=tetralogy of Fallot; [a]: Mann-Whitney U test; [b]: calculated using Dutch normative values[38]; [c]: calculated using the equation of Haycock *et al.*[39]; *P**: healthy versus ToF; *P*^#^: healthy versus Fontan; *P*^†^: ToF versus Fontan; *: *P*<0.05; **: *P*<0.01; ***: *P*<0.001.

Results

Participant characteristics of the healthy children, ToF patients, and Fontan patients are shown in TABLE 6. Body height, body mass, and BSA were significantly lower in Fontan patients compared to their healthy peers. Moreover, Fontan patients were younger, underwent their first surgical procedure at a younger age, and had significantly lower values for body height, body mass, and BSA compared to ToF patients. No significant anthropometric differences between ToF patients and their healthy peers were found. A normal BMI for age was found in all three groups.

All participants exercised to maximal exertion without any adverse events. They all performed a sufficient level of effort indicated by an RER_{peak} >1.0. CPET results are shown in TABLE 7. HR_{peak} was significantly lower in the children with CHD compared to their healthy counterparts; however, it was not significantly different between ToF patients and Fontan patients. The Spo_2 at rest and at peak exercise (Spo_{2peak}) was significantly lower in Fontan patients compared to ToF patients and the healthy participants, whereas only Spo_{2peak} was significantly lower in ToF patients compared to the healthy children. Work rate at peak exercise (WR_{peak}) normalized for body mass appeared to be significantly higher in the healthy group. As expected, a significant difference has been found within CHD patients, with

significantly lower WR_{peak} values normalized for body mass in Fontan patients compared to ToF patients. Significantly lower values for $V\dot{O}_{2peak}$ normalized for body mass were attained within the CHD group compared to their healthy peers. Within the total group of CHD patients, Fontan patients accomplished significantly lower $V\dot{O}_{2peak}$ values adjusted for body mass compared to ToF patients. The VT was found to be significantly reduced in Fontan patients compared to both ToF patients and healthy participants, whereas no significant difference was found between ToF patients and healthy children. The $V\dot{E}/V\dot{C}O_2$-slope was significantly increased in Fontan patients compared to both ToF patients and the healthy controls.

TABLE 7. CPET results.

	Healthy *(n=46)*	**ToF** *(n=15)*	***P****	**Fontan** *(n=16)*	$P^{\#}$	$P^{\dagger}$
HR_{peak} (beats·min^{-1})	193 ± 7	175 ± 21	<0.001 ***	166 ± 19	<0.001 ***	*NS*
RER_{peak}	1.15 ± 0.07	1.24 ± 0.11	0.008 **	1.15 ± 0.13	*NS*	0.009 **
SpO_2 at rest (%)	98.3 ± 1.7	98.3 ± 2.5	*NS*	94.1 ± 4.8	<0.001 ***	0.001 **
SpO_{2peak} (%)	97.1 ± 2.4	94.6 ± 4.2	0.029 *	87.1 ± 8.2	<0.001 ***	0.007 **
WR_{peak} (W·kg^{-1})	4.0 ± 0.6	3.5 ± 0.6	0.029 *	2.7 ± 0.7	<0.001 ***	0.002 **
$V\dot{O}_{2peak}$ (mL·kg^{-1}·min^{-1})	49.1 ± 7.7	40.9 ± 6.1	<0.001 ***	32.8 ± 9.1	<0.001 ***	0.002 **
$V\dot{E}_{peak}$ (L·kg^{-1}·min^{-1})	1.7 ± 0.3	1.5 ± 0.3	0.024 *	1.4 ± 0.5	0.002 **	*NS*
VT (mL·min^{-1})	1488 ± 479	1257 ± 393	*NS*	797 ± 168	<0.001 ***	0.001 **
$V\dot{E}/V\dot{C}O_2$-slope	29.8 ± 3.6	28.4 ± 5.2	*NS*	36.0 ± 5.7	<0.001 ***	0.001 **
$V\dot{E}/V\dot{O}_2$-slope	37.3 ± 6.1	34.7 ± 8.1	*NS*	42.0 ± 8.2	*NS*	0.013 *
OUES 100/BSA	1576 ± 286	1374 ± 262	0.024 *	1108 ± 234	<0.001 ***	0.008 **
OUES 75/BSA	1569 ± 301	1381 ± 287	0.038 *	1110 ± 213	<0.001 ***	0.013 *
OUES VT/BSA	1570 ± 307	1357 ± 260	0.006 **	1084 ± 236	<0.001 ***	0.010 *

Data are presented as mean ± SD.

ABBREVIATIONS: BSA=body surface area; CPET=cardiopulmonary exercise testing; HR_{peak}=peak heart rate; NS=not significant; OUES=oxygen uptake efficiency slope; RER_{peak}=peak respiratory exchange ratio; SD=standard deviation; $SpO_{2(peak)}$: peripheral measured oxygen saturation (at peak exercise); ToF=tetralogy of Fallot; $V\dot{E}_{peak}$=peak minute ventilation; $V\dot{E}/V\dot{C}O_2$-slope=regression coefficient of the relationship between the minute ventilation and the carbon dioxide production; $V\dot{E}/V\dot{O}_2$-slope=regression coefficient of the relationship between the minute ventilation and the oxygen uptake; $V\dot{O}_{2peak}$=peak oxygen uptake; VT=ventilatory threshold; WR_{peak}: peak work rate; P^{*}: healthy versus ToF; $P^{\#}$: healthy versus Fontan; $P^{\dagger}$: ToF versus Fontan; *: $P<0.05$; **: $P<0.01$; ***: $P<0.001$.

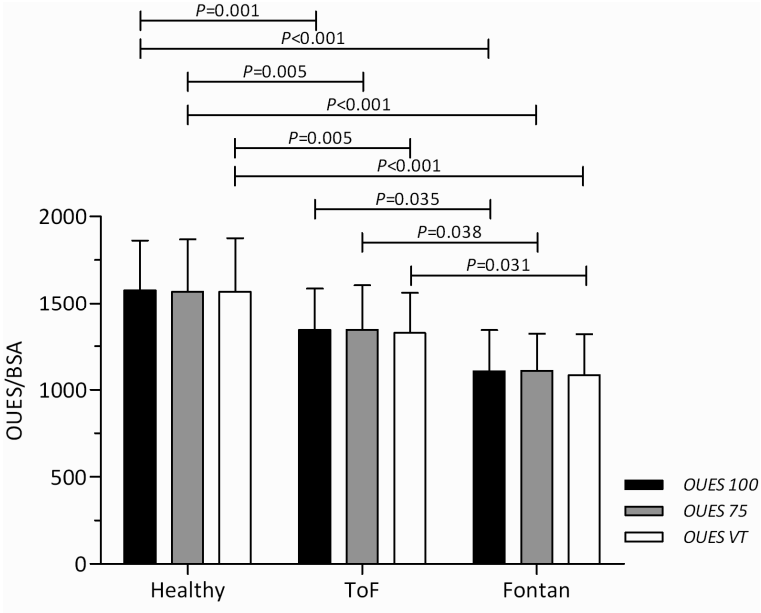

FIGURE 8. OUES values normalized for BSA at different exercise intensities in the healthy children, ToF patients, and Fontan patients.

Data are presented as mean + SD.

ABBREVIATIONS: BSA=body surface area; OUES=oxygen uptake efficiency slope; SD=standard deviation; ToF=tetralogy of Fallot; VT=ventilatory threshold.

As depicted in FIGURE 8 and TABLE 7, the OUES 100, OUES 75, and OUES VT were not significantly different between each other within all three groups. However, the absolute OUES values showed a large variation within each group, which was reduced using normalization for BSA. The OUES/BSA was significantly lower in the children with CHD compared to the healthy children, and within CHD, significantly lower values were observed in the Fontan patients compared to ToF patients. ROC analysis showed that the OUES 75/BSA had a sensitivity of 64% and specificity of 87% to differentiate between patients with CHD and healthy children, using a OUES cut-off value of 83% of predicted (area under the curve: 0.816, $P<0.001$).

As can be appreciated from TABLE 8, the OUES 100/BSA and OUES 75/BSA correlated significantly with the $V\text{O}_{2\text{peak}}$ normalized for body mass (r ranging from 0.571 to 0.611), VT (r ranging from 0.624 to 0.775), and $V\text{E}/V\text{CO}_2$-slope (r ranging from -0.574 to -0.750) in patients with CHD. However, the $V\text{O}_{2\text{peak}}$ adjusted for body mass did not correlate significantly (r=0.435, with $P>0.05$) with the OUES 75/BSA in Fontan patients. In addition, only the VT correlated significantly with the OUES

VT/BSA (r=0.536) in Fontan patients, whereas both the VT (r=0.557) and the $V\dot{O}_{2peak}$ adjusted for body mass (r=0.750) were significantly correlated with the OUES VT/BSA in ToF patients. No significant association was observed between the OUES and the drop in SpO_2 during CPET. Overall, associations weakened when a smaller amount of data points were used for the calculation of the OUES, with the OUES VT having the lowest correlation coefficients with other exercise parameters.

Discussion

The aim of the present study was to investigate the construct and group validity of the OUES in pediatric patients with CHD. Assessing its construct validity, it was found that the OUES values, calculated at three different exercise intensities, did not differ from each other. This demonstrates the linear relationship between the $V\dot{O}_2$ and the logarithm of the V_E throughout progressive CPET in both healthy children and children with CHD. It is in line with other studies in various patient groups to claim that the OUES is an effort-independent measure of aerobic exercise capacity.[13,15,19,22–24,42–45] This is an essential characteristic when a patient is either unwilling or unable to deliver a maximal effort during CPET.

The only study[19] that previously investigated the OUES characteristics in children with CHD reported a slightly, however significantly, lower OUES 75 compared to the OUES 100, which seems to be inconsistent with the findings in the current study. However, the authors made no distinction between healthy children and children with CHD.

The only study[36] that examined the OUES characteristics in adult patients with CHD reported, in agreement with the current study, significantly lower $V\dot{O}_{2peak}$ and OUES values, and significantly higher $V_E/V\dot{C}O_2$-slope values in Fontan patients compared to both healthy controls and patients who underwent a Mustard or Senning repair for transposition of the great arteries (TGA). Contrary to the current results, the authors found a nonlinear relationship between the $V\dot{O}_2$ and the logarithm of the V_E throughout CPET within Fontan patients. However, subgroup analysis revealed that this nonlinearity of the OUES was only present in cyanotic Fontan patients (SpO_2 at rest <95%). A post hoc analysis in the current study showed that the OUES maintains its linearity throughout CPET in Fontan patients who have a SpO_2 at rest <95% (n=8). Other studies investigating the linearity of the

TABLE 8. Spearman correlation coefficients between the OUES and other exercise parameters in CHD.

		ToF *(n=15)*	
	OUES 100/BSA	**OUES 75/BSA**	**OUES VT/BSA**
VO_{2peak} (mL·kg^{-1}·min^{-1})	0.611 *P*=0.016	0.571 *P*=0.026	0.750 *P*=0.001
VT (mL·min^{-1})	0.775 *P*=0.001	0.704 *P*=0.003	0.557 *P*=0.031
VE/VCO_2-slope	-0.639 *P*=0.010	-0.668 *P*=0.007	-0.400 *NS*
SpO_2 drop (%)	0.027 *NS*	0.236 *NS*	0.396 *NS*

		Fontan *(n=16)*	
	OUES 100/BSA	**OUES 75/BSA**	**OUES VT/BSA**
VO_{2peak} (mL·kg^{-1}·min^{-1})	0.606 *P*=0.013	0.435 *NS*	0.324 *NS*
VT (mL·min^{-1})	0.652 *P*=0.006	0.624 *P*=0.010	0.536 *P*=0.032
VE/VCO_2-slope	-0.750 *P*=0.001	-0.574 *P*=0.020	-0.456 *NS*
SpO_2 drop (%)	-0.150 *NS*	-0.211 *NS*	-0.374 *NS*

ABBREVIATIONS: BSA=body surface area; CHD=congenital heart disease; NS=not significant; OUES=oxygen uptake efficiency slope; SpO_2=peripheral measured oxygen saturation; ToF=tetralogy of Fallot; VE/VCO_2-slope=regression coefficient of the relationship between the minute ventilation and the carbon dioxide production; VO_{2peak}=peak oxygen uptake; VT=ventilatory threshold.

OUES in adult patients with heart disease confirm the current results by concluding that the OUES remains relatively stable over the entire exercise duration (in heart failure[13,15,20,24,26,28] and coronary artery disease[35]), while others found that the OUES using the first 50% of the exercise data (heart failure[23]) and the OUES determined using exercise data up to RER=1.0 (coronary artery disease[32]) differed significantly from the OUES 100.

The OUES was significantly related to other indices of aerobic exercise capacity (VO_{2peak} and the VT), showing its construct validity as well. However, associations weakened when a smaller amount of data points were used for the calculation of the OUES, with the OUES VT having the lowest correlation coefficients with other exercise parameters. These correlations are slightly lower compared to those between both the OUES 100 and OUES 75 with the VO_{2peak} (r=0.941 and r=0.946 respectively) in children with CHD reported by Baba *et al.*[19] The associations found by Giardini *et al.*[36] between the OUES calculated at different exercise intensities and the VO_{2peak} in adult patients with CHD were slightly higher as well (r values ranging from 0.812 to 0.922 within Mustard and Senning patients and from 0.719 to 0.891 within Fontan patients). Confirming the current results, the correlations in the latter study appeared to be weaker using only the first 50% of the exercise data (r=0.719).

The current study showed that children with CHD attained significantly lower OUES values compared to healthy children. Even within the total group of children with CHD, significantly lower OUES values were observed for Fontan patients compared to ToF patients. Thus, the OUES possessed sufficient discriminative power to distinguish between patients with CHD and their healthy counterparts (group validity). The lower OUES values can be explained by the significantly increased V_E/V_{CO_2}-slope in Fontan patients, which indicates a significant ventilation-perfusion mismatch,[46] resulting in an increased ventilatory dead space ventilation (V_D/V_T ratio).[47] Patients with ToF might also have a persistent ventilation-perfusion mismatch and/or the inability to increase pulmonary blood flow appropriately with exercise.[48] Moreover, just as in Fontan patients, the velocity of the increase of V_{O_2} at the onset of exercise is slowed,[49] increasing the dependency on anaerobic energy utilization. Together with the impaired skeletal muscle metabolism in chronic heart failure,[50] this causes a higher contribution from anaerobic glycolysis (metabolic acidosis) at lower work rate values, which is reflected by the reduced VT within Fontan patients in this study. Indeed, these above mentioned factors might explain the reduced OUES values in CHD, since the OUES is physiologically based on the V_D/V_T ratio and the point where lactic acid begins to accumulate.[19–21,26]

The OUES appears to be a useful parameter of aerobic exercise capacity in children with CHD. However, in the authors' opinion, the OUES has not been introduced in order to predict $V_{O_{2peak}}$ or to act as a substitute for $V_{O_{2peak}}$ measurements. Therefore, interpretation of OUES values should be based on adequate reference values, comparison between (groups of) individuals, or comparisons within individuals (e.g. in order to evaluate the cardiopulmonary response to a specific training regime). Additionally, maximal CPET yields specific information regarding adaptations of the cardiopulmonary system during progressive exercise (e.g. development of exercise-induced arrhythmias, development of exercise-induced ischemia, assessment of anti-arrhythmic drug efficacy), which does not always occur during submaximal exercise testing. Thus, although the OUES is an effort-independent measure of aerobic exercise capacity, which adds useful information about the cardiopulmonary response during progressive exercise, it remains unknown whether the OUES provides information beyond that of the more established measures such as $V_{O_{2peak}}$ and the VT.

The current study has some limitations. The patients with CHD who were referred for CPET had undergone completion of Fontan circulation or repair for ToF from a single tertiary center. This could have led to a biased sample. In addition, there was a large, unavoidable, heterogeneity in the physiology of the studied patients.

Although this heterogeneity makes exact comparison difficult, the currently included patients are representative for a tertiary children's hospital, which strengthens the generalization of the current findings. Furthermore, the sample of CHD patients included only Fontan and ToF patients. Whether the OUES is a valid indicator of aerobic exercise capacity in other pediatric CHD patient groups (e.g. TGA, cardiac shunts, pulmonary hypertension) needs further investigation.

As recommended previously,[41] it is advised to normalize OUES values for BSA, since this reduces the variability in OUES values to the greatest extent. Moreover, normalization compensates for the development of body size in children due to growth and maturation. Furthermore, associations with other exercise variables weakened when a smaller amount of data points were used for its determination. Therefore, it seems to be important that the child continues exercising as long as possible towards his peak level, in order to gain as many data points for the calculation of the OUES.

In conclusion, the current study provides evidence that the OUES has a good construct and group validity in children with CHD. It proved to be independent of exercise intensity and was strongly correlated with $V_{O_{2peak}}$ and the VT (construct validity). Moreover, the OUES was found to be capable of differentiating between healthy children and children with CHD, and, within CHD, between Fontan patients and ToF patients (group validity). Therefore, the OUES could be used as a valid, objective, and effort-independent measure of aerobic exercise capacity in children with CHD.

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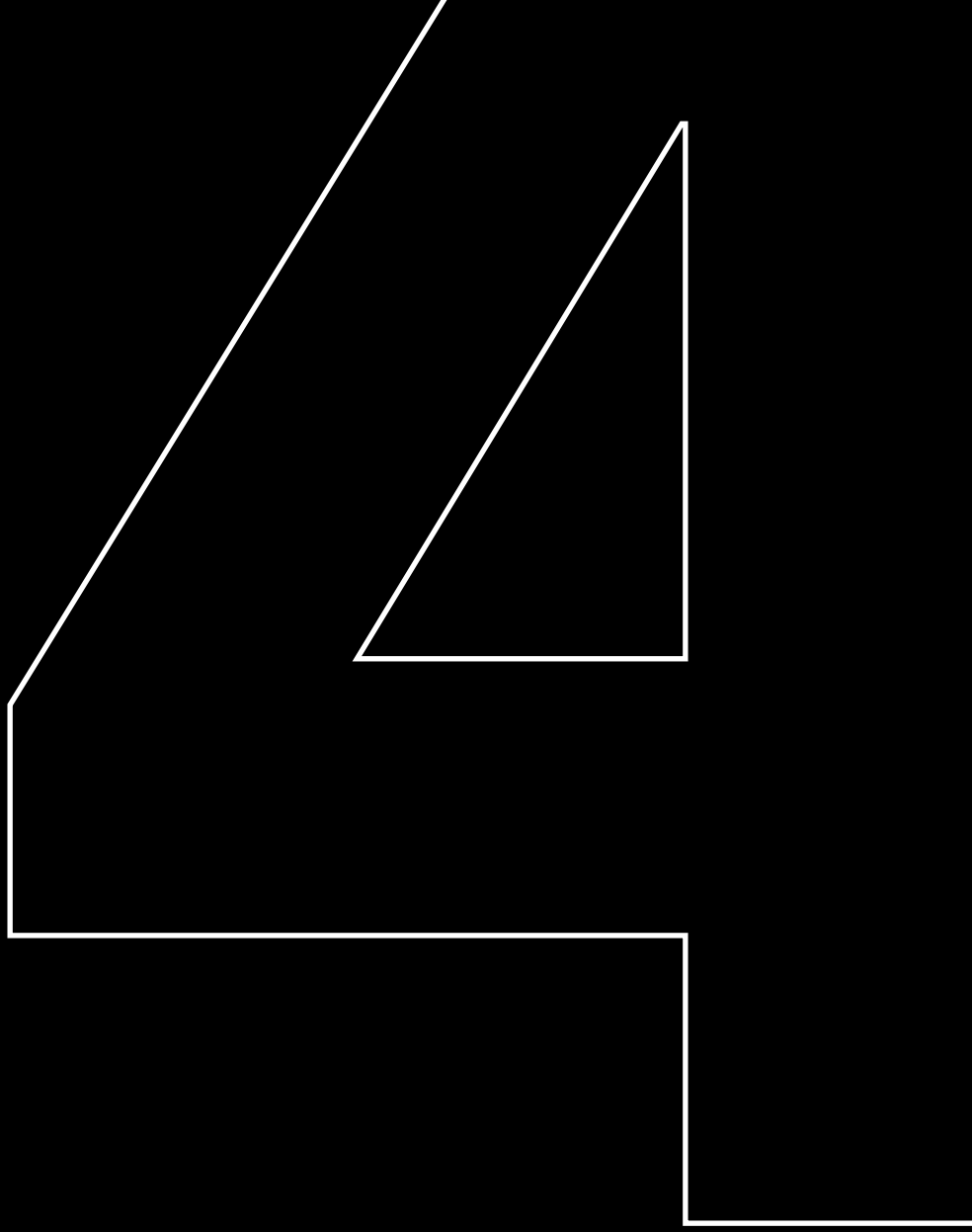

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Pediatric Exercise Science
2012;24:129-41

Validity of the oxygen uptake efficiency slope in children with cystic fibrosis and mild-to-moderate airflow obstruction

Abstract

Background

The oxygen uptake efficiency slope (OUES) has been introduced as an 'effort-independent' measure of aerobic exercise capacity, which could be used as an alternative measurement for peak oxygen uptake (VO_{2peak}) in populations unable or unwilling to perform maximal exercise. The aim of the current study was to investigate the validity of the OUES in children with cystic fibrosis (CF).

Methods

Exercise data of 22 children with CF and mild to moderate airflow obstruction (13 boys and 9 girls, mean ± standard deviation [SD] age: 15.7 ± 1.5) were analyzed and compared to exercise data of 22 healthy children (13 boys and 9 girls, mean ± SD age: 14.2 ± 1.5). The OUES was calculated using data up to three different relative exercise intensities, namely 50%, 75%, and 100% of the total exercise duration, and normalized for body surface area (BSA).

Results

Only the OUES/BSA using the first 50% of the total exercise duration was significantly different between the groups (1378 ± 295 versus 1616 ± 333; P=0.016), despite the fact that VO_{2peak} was significantly reduced in patients with CF (40.9 ± 7.8 versus 49.9 ± 7.9 $mL \cdot kg^{-1} \cdot min^{-1}$; P<0.001). OUES/BSA values determined at different exercise intensities differed significantly within patients with CF (1378 ± 295, 1542 ± 328, and 1610 ± 336 using the first 50% of the exercise data, using the first 75% of the exercise data, and using 100% of the exercise data respectively). By performing a post hoc analysis, it was demonstrated that the latter results can be explained by the fact that the efficiency of ventilation in children with moderate CF was significantly reduced during submaximal exercise when compared to their healthy peers. During the last part of CPET, the children with CF approached the values for the efficiency of ventilation attained by their healthy peers. Nevertheless, the OUES/BSA correlated only moderately with VO_{2peak} (r values ranging from 0.411 to 0.536; with P<0.05 for all coefficients) and the ventilatory threshold (r values ranging from 0.350, not significant, to 0.541; with P<0.05 for the other coefficients).

Conclusion

The OUES is not a valid submaximal measure of aerobic exercise capacity in children with mild to moderate CF, due to its limited distinguishing properties, its nonlinearity throughout progressive exercise, and its moderate correlation with VO_{2peak} and the ventilatory threshold.

Introduction

Aerobic exercise capacity, as measured during incremental cardiopulmonary exercise testing (CPET), is a good prognostic factor for survival in patients with cystic fibrosis (CF).[1] The maximal oxygen uptake ($V\dot{O}_{2max}$) is generally considered the most reliable single measure of an individual's aerobic exercise capacity, reflecting the highest rate at which someone can consume oxygen during exercise with large muscle groups.[2] Classically, $V\dot{O}_{2max}$ requires a maximal effort with the leveling-off of oxygen uptake ($V\dot{O}_2$), despite continuing exercise and increasing work rate (WR).[3] Many healthy children as well as patients do not show such a plateau in $V\dot{O}_2$ during exercise. However, since a number of authors[4,5] showed that this leveling-off of $V\dot{O}_2$ is not essential for defining the highest $V\dot{O}_2$ in children, this measure is often replaced by the peak $V\dot{O}_2$ ($V\dot{O}_{2peak}$), the highest $V\dot{O}_2$ measured during CPET.[3,6]

Questions can be raised about the validity of the $V\dot{O}_{2peak}$ in children with CF during maximal exercise.[7] Some authors have reported a reduced aerobic exercise capacity during CPET in children with CF compared to healthy peers.[8-11] However, the observed peak heart rates (HR_{peak}) in these studies were also significantly lower compared to values observed in healthy children. Therefore, this lower $V\dot{O}_{2peak}$ might be due to a truly lower $V\dot{O}_{2peak}$ or to an incapability of the patient to reach a true $V\dot{O}_{2peak}$. Moreover, the $V\dot{O}_{2peak}$ can be strongly influenced by the patient's motivation, the selected exercise protocol, and the experience of the tester.[3,12,13] Because of these limitations and the difficulty in performing a maximal effort during CPET, there has been a search for alternative indices that could be obtained without performing a maximal effort.

The oxygen uptake efficiency slope (OUES) might act as an alternative for the $V\dot{O}_{2peak}$.[14] The OUES describes the linear relationship between the $V\dot{O}_2$ and the common logarithm of the minute ventilation (V_E) throughout CPET. Theoretically, due to the linearity of the OUES throughout CPET, this measurement should be resistant to disruption by early termination during CPET.[3,15] Since the original rationale of the OUES was to provide a submaximal measure of aerobic exercise capacity, which could be used as a possible alternative for the $V\dot{O}_{2peak}$ in populations unable to perform maximal exercise, the aim of the current study was to investigate whether the OUES could be used as a valid, submaximal measure of aerobic exercise capacity in children with CF.

Methods

Participants

Anthropometry, lung function, and aerobic exercise capacity of children with CF were measured as part of regular evaluation measures during their annual medical check-up in the CF Center of the Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands. Data from patients with a stable clinical condition, no active musculoskeletal disorders, and a forced expiratory volume in one second (FEV_1) >30% predicted were analyzed. In addition, for each patient with CF, exercise data from a healthy child was examined. All healthy children were by definition free from chronic diseases, and were not on medication that might affect their exercise capacity. Informed consent was obtained from the parents and, if older than 12 years of age, from the children as well. The institution's medical ethics committee approved the study protocol.

Spirometry and plethysmography

In the patients with CF, spirometry and body plethysmography were performed using a pneumotach system and a volume-constant plethysmograph (Master Laboratory system; Jaeger, Würzburg, Germany), after bronchodilator inhalation (800 μg salbutamol). Forced vital capacity (FVC) and FEV_1 were obtained from maximal flow volume curves, after which the Tiffeneau index was calculated. The highest value for residual volume (RV) and the lowest value for total lung volume (TLC) were used to calculate the RV/TLC ratio (RV/TLC%) to evaluate air trapping.

Cardiopulmonary exercise testing

CPET was performed using an electronically braked cycle ergometer (Lode Corival; Lode, Groningen, the Netherlands). After assessment of baseline cardiopulmonary values during a three minute rest period, the test started with one minute of unloaded cycling. Thereafter, WR was increased by a constant increment of 15 or 20 $W \cdot min^{-1}$, according to the Godfrey protocol.[16] Participants were instructed to maintain a pedaling rate between 60 and 80 $revolutions \cdot min^{-1}$. Strong verbal encouragement was given until the patient stopped because of maximal exertion. Heart rate (HR) was monitored by a three-lead electrocardiogram (Hewlett-Packard, Amstelveen, the Netherlands), and peripheral oxygen saturation was measured at the index finger by pulse oximetry (Nellcor 200 E; Nellcor, Breda, the Netherlands). During CPET, participants breathed continuously through a

facemask (Hans Rudolph Inc, Kansas City, MO, USA). Breath-by-breath respiratory gas analysis and volume measurements were performed with gas analyzers for oxygen and carbon dioxide (Jaeger Oxycon Pro; Care Fusion, Houten, the Netherlands) and a flow meter (Triple V volume transducer). Output from the gas analyzers and flow meter were averaged at ten-second intervals and stored for further use. Effort was considered to be at a maximal level when the participant showed clinical signs of intense effort and was unable to maintain the required pedaling rate, and when at least one of the following criteria was met: an HR_{peak} >180 beats·min^{-1} or a respiratory exchange ratio (RER) at peak exercise (RER_{peak}) >1.0.[17]

Calculations

Peak exercise variables were taken as the average value during the last 30 seconds of CPET. Minute ventilation (V_E), V_{O_2}, carbon dioxide output (V_{CO_2}), and the RER were calculated from conventional equations. The estimated ventilatory dead space ventilation (V_D/V_T ratio) was calculated by using the end-tidal partial pressure of carbon dioxide. The ventilatory threshold (VT) was determined according to the V-slope method, and was expressed as a percentage of $V_{O_{2peak}}$ (VT%) as well. The regression coefficient of the relationship between the V_E and the V_{O_2} (V_E/V_{O_2}-slope), as well as the regression coefficient of the relationship between the V_E and the V_{CO_2} (V_E/V_{CO_2}-slope) were calculated using all exercise data. The OUES was calculated using exercise data up to three different exercise intensities according to the equation of Baba *et al.*[14] (see *CHAPTER 1*). For the determination of the OUES 100, all data gathered during CPET were used, whereas for the determination of the OUES 75 and the OUES 50, only data up to 75% and 50% respectively of the total exercise duration were used. To reduce the variability between participants due to growth and maturation, body surface area (BSA) was used to normalize OUES values (OUES/BSA).[18]

Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS version 15.0; SPSS Inc., Chicago, IL, USA). Tests for normality were performed on the data with the Shapiro-Wilk test. As appropriate, independent samples t-tests or Mann-Whitney U tests were performed on the anthropometric and the exercise variables to test for significant differences between the two groups. Repeated measures analysis of variance (ANOVA) was used to evaluate the differences in OUES/BSA values calculated at the three different exercise intensities within the two groups. Additional post hoc analyses with Bonferroni adjustment for multiple testing were performed on the outcomes of the repeated-measures ANOVA tests to

locate the exact significant differences. Pearson correlation coefficients were calculated to examine the relationship between exercise and lung function variables and the OUES/BSA. Significance was a priori set at the 0.05 level.

Results

Twenty-two children with CF and 22 healthy children, 11 – 18 years of age, 13 boys and 9 girls in each group, were included in this study. Participant characteristics are shown in TABLE 9. Anthropometric data between the two groups did not differ significantly. Children with CF were significantly older than the healthy controls (P=0.002), and they had a significantly lower body height for age and body mass for age standard deviation (SD) scores (P=0.006 and P=0.002 respectively). Lung function characteristics of the children with CF are shown in TABLE 10. With a FEV_1 of 81.52 ± 15.57% of predicted and an RV/TLC% of 35.78 ± 10.15%, CF patients suffered from mild to moderate airflow obstruction.

TABLE 9. Participant characteristics.

	Healthy *(n=22)*		**CF** *(n=22)*		
Sex (male/female)	13/9		13/9		
Age (years)	14.2 ± 1.5	[11.9 – 16.8]	15.7 ± 1.5	[11.8 – 18.7]	**
Body height (m)	1.67 ± 0.10	[1.45 – 1.91]	1.68 ± 0.09	[1.52 – 1.80]	
Body height for age SD score [a]	0.15 ± 0.88	[-1.33 – 2.15]	-0.69 ± 1.04	[-2.37 – 1.71]	**
Body mass (kg)	53.9 ± 12.1	[33.0 – 81.7]	53.9 ± 6.8	[35.0 – 63.0]	
Body mass for age SD score [a]	0.05 ± 0.86	[-1.48 – 2.05]	-0.69 ± 0.64	[-2.12 – 0.56]	**
Body mass for height SD score [a]	-0.04 ± 0.78	[-1.27 – 1.35]	-0.36 ± 0.92	[-1.89 – 1.31]	
BMI ($kg \cdot m^{-2}$)	19.2 ± 2.6	[15.7 – 25.5]	19.3 ± 1.9	[15.2 – 23.4]	
BMI for age SD score [a]	-0.02 ± 0.79	[-1.34 – 1.50]	-0.33 ± 0.74	[-1.56 – 1.06]	
BSA (m^2) [b]	1.57 ± 0.22	[1.14 – 2.02]	1.60 ± 0.14	[1.25 – 1.81]	

Data are presented as mean ± SD, [range].

ABBREVIATIONS: BMI=body mass index; BSA=body surface area; CF=cystic fibrosis; SD=standard deviation; [a]: calculated using Dutch normative values[19]; [b]: calculated using the equation of Haycock *et al.*[20]; **: P<0.01.

TABLE 10. Lung function characteristics of the children with CF.

	CF *(n=22)*	
FVC (L)	3.83 ± 0.83	[2.20 – 4.99]
FVC (% of predicted) [a]	*97 ± 11*	*[60 – 107]*
FEV_1 (L)	2.71 ± 0.65	[1.43 – 4.03]
FEV_1 (% of predicted) [a]	*82 ± 16*	*[46 – 107]*
Tiffeneau index	0.72 ± 0.15	[0.53 – 1.12]
Tiffeneau index (% of predicted) [a]	*85 ± 18*	*[63 – 133]*
RV (L)	1.91 ± 0.55	[1.06 – 3.40]
RV (% of predicted) [a]	*167 ± 46*	*[103 – 298]*
TLC (L)	5.38 ± 0.91	[3.26 – 6.79]
TLC (% of predicted) [a]	*106 ± 11*	*[85 – 126]*
RV/TLC%	35.78 ± 10.15	[21.59 – 65.38]
RV/TLC% (% of predicted) [a]	*153 ± 42*	*[93 – 276]*

Data are presented as mean ± SD, [range].

ABBREVIATIONS: CF=cystic fibrosis; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; RV=residual volume; RV/TLC%=ratio of the residual volume to the total lung volume; SD=standard deviation; TLC=total lung volume; [a]: calculated using reference values from Zapletal.[21]

All participants terminated CPET due to maximal exertion, without adverse effects. CPET results are presented in TABLE 11. In the patients with moderate CF, significantly higher values for RER_{peak} were found (P=0.037), and significantly lower values for peak WR (WR_{peak}) (P<0.001), absolute V_{O2peak} (P=0.020), relative V_{O2peak} (P<0.001), relative V_{O2peak} expressed as a percentage of predicted (P=0.001), and VT (P=0.031) were found. Patients with moderate CF also had a significantly higher estimated V_D/V_T ratio at peak exercise (P<0.001). HR_{peak} and peak V_E ($V_{E\text{-}peak}$) values were not significantly different between children with moderate CF and their healthy peers. The VT occurred at an average of ~67% of V_{O2peak} in both groups.

The mean values of the absolute OUES 100, OUES 75, and OUES 50 in the children with moderate CF were 2598.7 ± 642.9, 2487.1 ± 610.5, and 2220.1 ± 546.1 respectively (2703.9 ± 637.2; 2664.1 ± 695.1, and 2547.2 ± 685.6 for the healthy controls respectively; no significant between group differences). Concerning the capability of the OUES to distinguish between healthy children and children with moderate CF, only the OUES 50/BSA appeared to be significantly different between the two groups (see FIGURE 9), with lower values achieved in the children with moderate CF (P=0.016). FIGURE 9 also shows the effect of exercise duration on the OUES/BSA, thereby showing its linearity characteristics within the two groups.

TABLE 11. CPET results.

	Healthy (n=22)		CF (n=22)		
HR_{peak} (beats·min^{-1})	192 ± 7	[180 – 204]	188 ± 9	[166 – 206]	
RER_{peak}	1.15 ± 0.06	[1.01 – 1.28]	1.20 ± 0.10	[0.96 – 1.37]	*
WR_{peak} (W·kg^{-1})	4.1 ± 0.6	[2.6 – 5.0]	3.4 ± 0.5	[2.6 – 4.7]	***
$\dot{V}O_{2peak}$ (mL·min^{-1})	2677 ± 699	[1725 – 4140]	2222 ± 547	[1368 – 3304]	*
$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	49.9 ± 7.9	[33.6 – 62.9]	40.9 ± 7.8	[29.2 – 61.8]	***
$\dot{V}O_{2peak}$ (% of predicted) [a]	*112 ± 19*	*[72 – 144]*	*92 ± 18*	*[66 – 132]*	**
$\dot{V}E_{peak}$ (L·min^{-1})	91.9 ± 28.1	[44.6 – 149.5]	87.5 ± 22.0	[47.0 – 139.0]	
$\dot{V}E_{peak}$ (L·kg^{-1}·min^{-1})	1.7 ± 0.4	[0.8 – 2.4]	1.6 ± 0.3	[0.9 – 2.3]	
Estimated peak $\dot{V}D/\dot{V}T$ ratio (%)	16.8 ± 1.8	[11.7 – 19.3]	23.0 ± 4.0	[15.7 – 30.3]	***
VT (mL·min^{-1})	1794 ± 488	[1166 – 2767]	1492 ± 408	[781 – 2465]	*
VT% (% of $\dot{V}O_{2peak}$)	67 ± 8	[58 – 87]	67 ± 9	[50 – 78]	

Data are presented as mean ± SD, [range].

ABBREVIATIONS: CF=cystic fibrosis; CPET=cardiopulmonary exercise testing; HR_{peak}=peak heart rate; RER_{peak}=peak respiratory exchange ratio; SD=standard deviation; $\dot{V}D/\dot{V}T$ ratio=physiological dead space ventilation; $\dot{V}E_{peak}$=peak minute ventilation; $\dot{V}O_{2peak}$=peak oxygen uptake; VT=ventilatory threshold; VT%=ventilatory threshold expressed as a percentage of peak oxygen uptake; WR_{peak}=peak work rate; [a]: calculated using reference values from ten Harkel *et al.*[22]; *: P<0.05; **: P<0.01; ***: P<0.001.

The OUES 50/BSA in children with moderate CF appeared to be significantly lower than both the OUES 75/BSA (8.86%) and the OUES 100/BSA (12.69%). In addition, the OUES 75/BSA was significantly lower than the OUES 100/BSA (4.20%). In contrast, no significant within group differences were found between the OUES 100/BSA, OUES 75/BSA, and OUES 50/BSA in the healthy children.

Correlations between the OUES/BSA, determined at different relative exercise intensities, and exercise and lung function variables, are summarized in TABLE 12. In children with moderate CF, the OUES/BSA correlated moderately with the relative $\dot{V}O_{2peak}$ (r values ranging from 0.411 to 0.536), relative $\dot{V}O_{2peak}$ expressed as a percentage of predicted (r values ranging from 0.385 to 0.511), and with the VT (r values ranging from 0.350 to 0.541). In the healthy children, moderate to strong correlations were found between the OUES/BSA and the relative $\dot{V}O_{2peak}$ (r values ranging from 0.547 to 0.781), relative $\dot{V}O_{2peak}$ expressed as a percentage of predicted (r values ranging from 0.395 to 0.632), and the VT (r values ranging from 0.552 to 0.774). Overall, associations weakened when a smaller amount of data points were used for the calculation of the OUES, with OUES 50/BSA having the lowest correlation coefficients with the relative $\dot{V}O_{2peak}$ and the VT. No significant associations were observed between the OUES/BSA and lung function parameters.

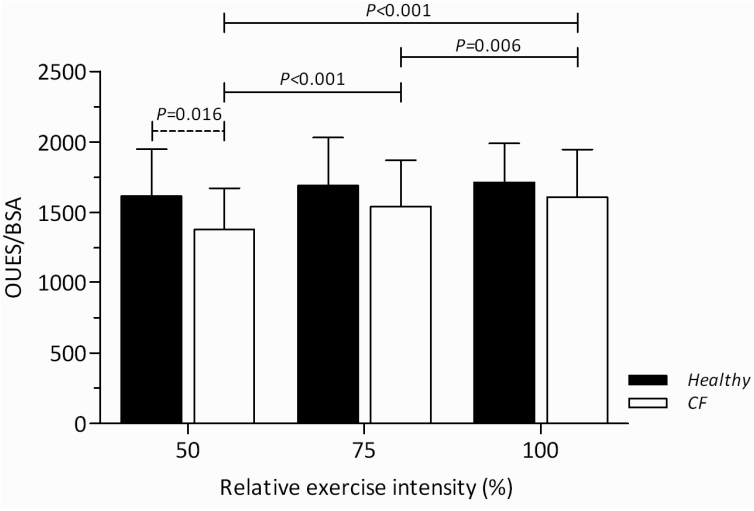

FIGURE 9. The OUES values normalized for BSA at the three different relative exercise intensities (% of total exercise duration).

Data are presented as mean + SD.
ABBREVIATIONS: BSA=body surface area; CF=cystic fibrosis; OUES=oxygen uptake efficiency slope; SD=standard deviation.

A post hoc analysis was performed to elucidate the nonlinearity of the OUES/BSA in patients with CF. The $\dot{V}O_2$, common logarithm of the $\dot{V}E$ (Log $\dot{V}E$), $\dot{V}E$, $\dot{V}E/\dot{V}O_2$-slope, $\dot{V}E/\dot{V}CO_2$-slope, and the estimated V_D/V_T ratio were obtained at 50%, 75%, and 100% of the total exercise duration as the average value of 30 seconds (see FIGURE 10 and TABLE 13). FIGURE 10 illustrates that the Log $\dot{V}E$ (left graph) appeared to be similar in both groups at 50% of the total exercise duration, while patients with CF achieved lower, but not significantly lower, Log $\dot{V}E$ values at 75% and 100% of the total exercise duration (P=0.191 and P=0.291 respectively). In contrast, FIGURE 10 demonstrates significantly lower $\dot{V}O_2$ values (right graph) attained by the children with CF at all three different relative exercise intensities (P=0.007, P=0.011, and P=0.022 at 50%, 75%, and 100% of the total exercise duration respectively), in which the differences between both groups remained relatively constant. TABLE 13 confirms these findings with the $\dot{V}E$ and the $\dot{V}O_2$, both normalized for body mass. TABLE 13 also shows that corresponding to the observation of a significantly lower OUES 50/BSA (see FIGURE 9, P=0.016), these findings lead to a significantly higher $\dot{V}E/\dot{V}O_2$-slope at 50% of the exercise duration in children with CF (P=0.036). Accompanying analysis revealed that during the entire range of CPET, children with CF had significantly higher RER values (data not shown), in which the largest differences were found at rest and during low-intensity exercise.

TABLE 12. Pearson correlation coefficients between the OUES normalized for BSA at the three different relative exercise intensities and different exercise and lung function variables.

	OUES 50/BSA		OUES 75/BSA		OUES 100/BSA	
	Healthy	**CF**	**Healthy**	**CF**	**Healthy**	**CF**
VO_{2peak} (mL·kg^{-1}·min^{-1})	0.547 **	0.411	0.707 **	0.466 *	0.781 **	0.536 *
VO_{2peak} (% of predicted) [a]	0.395	0.385	0.544 *	0.447 *	0.632 **	0.511 *
VT (mL·min^{-1})	0.552 **	0.350	0.730 **	0.459 *	0.774 **	0.541 **
VE/VCO_2-slope	-0.100	-0.416	-0.148	-0.430 *	-0.213	-0.405
Estimated VD/VT ratio (%)	0.441 *	0.133	0.427 *	0.263	0.366	0.239
FEV_1 (% of predicted) [b, c]	*NA*	-0.085	*NA*	-0.119	*NA*	-0.114
Tiffeneau index [b]	*NA*	-0.212	*NA*	-0.263	*NA*	-0.324
RV/TLC% [b]	*NA*	-0.059	*NA*	-0.107	*NA*	-0.215

Abbreviations: BSA=body surface area; CF=cystic fibrosis; FEV_1=forced expiratory volume in one second; NA=not applicable; OUES=oxygen uptake efficiency slope; RV/TLC%=ratio of the residual volume to the total lung volume; VD/VT ratio=physiological dead space ventilation; VE/VCO_2-slope=regression coefficient of the relationship between the minute ventilation and the carbon dioxide production; VO_{2peak}=peak oxygen uptake; VT=ventilatory threshold; [a]: calculated using reference values from ten Harkel *et al.*[22]; [b]: variables not measured in the healthy participants; [c]: calculated using reference values from Zapletal.[21]; *: $P<0.05$; **: $P<0.01$.

Discussion

To the authors' knowledge, this is the first study that investigated the characteristics of the OUES/BSA in children with CF and mild to moderate airflow obstruction, and that compared these values to values obtained by healthy children. The main findings implicate that even though children with moderate CF had a significantly reduced VO_{2peak} normalized for body mass, only the OUES 50/BSA was significantly lower in patients with moderate CF. Moreover, the OUES depended on exercise intensity in the children with moderate CF due to its nonlinearity during the last part of CPET. Further, the OUES correlated only moderately with VO_{2peak} normalized for body mass and the VT in these patients.

When the OUES is calculated, the VE is logarithmically transformed to produce a linear relationship with VO_2, which makes it an exercise intensity independent measure that is resistant to disruption by early termination during CPET.[3,15] However, in contrast to the construct of the OUES and the healthy children, the OUES appeared to be nonlinear in the patients with moderate CF. A post hoc analysis

(see FIGURE 10 and TABLE 13) showed that both groups achieved similar V_E values at 50% of the total exercise duration (Log V_E and V_E normalized for body mass). However, children with moderate CF achieved a significantly lower V_{O_2} and V_{O_2} adjusted for body mass at this exercise intensity, resulting in a reduced efficiency of ventilation during submaximal exercise as specified by both the V_E/V_{O_2}-slope (see TABLE 13), and the OUES/BSA using exercise data up to 50% of the total exercise duration (see FIGURE 9). When exercise progressed to 75% and 100% of the total exercise duration, children with moderate CF maintained a significantly reduced V_{O_2} and V_{O_2} normalized for body mass (see FIGURE 10 and TABLE 13). However, children with moderate CF also ventilated less compared to their healthy peers at 75% and 100% of the total exercise duration (not statistically significant). As a consequence, the efficiency of ventilation in children with moderate CF approached values attained by their healthy peers, as indicated by the V_E/V_{O_2}-slope using 75% and 100% of the total exercise duration (see TABLE 13) and the OUES 75/BSA and OUES 100/BSA (see FIGURE 9).

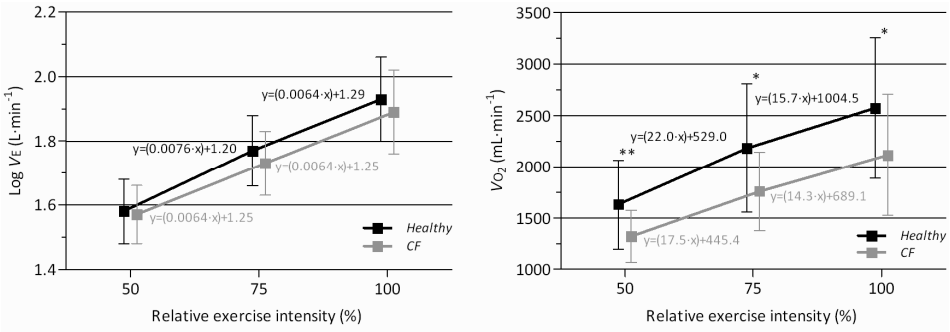

FIGURE 10. The components of the OUES, the Log V_E (left graph) and the V_{O_2} (right graph), determined at the three different relative exercise intensities (% of total exercise duration). For both groups regression lines with their regression coefficients are presented between the mean values at 50% of the exercise duration and the mean values at 75% of the exercise duration, as well as between the mean values at 75% of the exercise duration and the mean values at 100% of the exercise duration.

Data are presented as mean ± SD.

ABBREVIATIONS: CF=cystic fibrosis; Log V_E=common logarithm of the minute ventilation; OUES=oxygen uptake efficiency slope; SD=standard deviation; V_{O_2}=oxygen uptake; *: P<0.05; **: P<0.01.

Regardless of a clear rationale for its nonlinearity, the OUES seems to be an exercise intensity dependent measure in children with mild to moderate CF. Hence, the OUES seems to be invalid as an effort-independent measure of aerobic exercise capacity in children with mild to moderate CF. Gruet *et al.*[29] investigated the linearity characteristics of the OUES in adult patients with moderate CF and

reported a limited dependency on exercise duration. They determined the OUES using the first 50%, 60%, 70%, 80%, and 100% of the exercise duration. They found the OUES values determined at 50% and 60% to be significantly lower compared to the OUES values determined at higher exercise intensities. Previous studies conducted in other pediatric populations, including a study in healthy and obese children[30,31] and a study in healthy children and children with heart disease,[14] confirm the current findings concerning the nonlinearity of the OUES during the last part of CPET. In contrast, other studies found no differences between the OUES values at different exercise intensities in healthy children,[32] and in children with congenital heart disease.[33]

TABLE 13. Exercise variables at the three different relative exercise intensities (% of total exercise duration).

	50			75			100		
	Healthy	**CF**		**Healthy**	**CF**		**Healthy**	**CF**	
V_{O_2} (mL·kg^{-1}·min^{-1})	30.5 ± 6.0	24.5 ± 3.9	***	40.6 ± 8.5	32.6 ± 5.7	**	47.9 ± 7.9	39.2 ± 9.5	**
V_E (L·kg^{-1}·min^{-1})	0.73 ± 0.15	0.71 ± 0.13		1.14 ± 0.24	1.01 ± 0.18		1.66 ± 0.37	1.50 ± 0.37	
Estimated V_D/V_T ratio (%)	15.9 ± 2.1	21.6 ± 4.0	***	16.4 ± 1.8	22.1 ± 3.8	***	16.8 ± 1.8	23.0 ± 4.0	***
V_E/V_{O_2}-slope	21.9 ± 3.2	24.8 ± 5.4	*	27.8 ± 5.3	29.4 ± 4.4		34.4 ± 5.1	36.1 ± 5.7	
V_E/V_{CO_2}-slope [a]	24.7 ± 2.9	26.0 ± 3.8		25.7 ± 3.0	26.5 ± 3.1		28.0 ± 3.1	29.2 ± 3.8	

Data are presented as mean ± SD.

ABBREVIATIONS: CF=cystic fibrosis; SD=standard deviation; V_D/V_T ratio=physiological dead space ventilation; V_E=minute ventilation; V_E/V_{CO_2}-slope=regression coefficient of the relationship between the minute ventilation and the carbon dioxide production; V_E/V_{O_2}-slope=regression coefficient of the relationship between the minute ventilation and the oxygen uptake; V_{O_2}=oxygen uptake.; [a]: Mann-Whitney U test.; *: P<0.05; **: P<0.01; ***: P<0.001.

Regarding the distinguishing properties of the OUES, it was expected that the OUES would be significantly decreased in children with mild to moderate CF compared to their healthy peers. The OUES physiologically depends on the point where lactic acid begins to accumulate.[34] Patients with mild to moderate CF are likely to have a reduced aerobic exercise capacity,[9,27,35] leading to an earlier accumulation of lactic acid, which in theory affects the OUES negatively. A study of Klijn *et al.*[36] suggested a shift towards a lower contribution of aerobic energy production, and hence, a greater dependency on anaerobic energy utilization during exercise in children with mild to moderate CF. This will induce a reflex hyperventilation.[37] The lack of a concomitant increase in V_{O_2} together with the excessively increasing V_E will lower the OUES. The current study results indicate that VT% was not significantly different between the patients with mild to moderate CF (67.3%) and their healthy peers (67.2%). This might be due to the fact that the CF Center that participated in the current study, strongly stimulates physical activity in patients with CF. It has been documented that children with CF with higher physical activity levels have a

lower disease severity and a significantly better aerobic exercise capacity, anaerobic exercise capacity, nutritional status and a higher health related quality of life.[38] Moreover, a higher aerobic exercise capacity has been associated with a significantly lower mortality in CF.[1] In addition, the OUES physiologically depends on the V_D/V_T ratio.[34] An increased V_D/V_T ratio will importantly influence the ventilatory response to exercise[3] leading to a reduced OUES. It has been reported that patients with mild or moderate CF are wasting ventilation during exercise because of a higher V_D/V_T ratio.[39,40] In this study, children with mild to moderate CF had a stable, but significantly higher estimated V_D/V_T ratio throughout the last part of CPET.

Only the OUES 50/BSA was significantly lower in patients with mild to moderate CF, despite the above stated hypothesis concerning a reduced OUES in CF, and the current study outcomes of both a reduced $V_{O_{2peak}}$ and an increased estimated V_D/V_T ratio. In contrast with the current study, a recent study conducted in adult patients with CF[29] reported significantly lower OUES values in adult patients with moderate CF. Hollenberg *et al*.[3] also found significantly reduced OUES values in participants with a decreased FEV_1. The CF patients in the current study had a mean percentage of predicted FEV_1 of 81.5%, which is considered to be mild airway obstruction.[41] A possible explanation for the current results is that although the included patients with mild to moderate CF had a significantly reduced $V_{O_{2peak}}$, and an increased estimated V_D/V_T ratio, they were not enough ventilatory limited during CPET to cause a significantly reduced OUES. Whether the OUES is a valid indicator of aerobic exercise capacity in a sample of (older) patients with more severe CF needs additional research.

A limitation of the study was the relatively small sample size, including mainly patients with CF with mild to moderate airflow obstruction. For this reason, these findings cannot be generalized to patients with severe airflow obstruction. Nevertheless, the current study sample is representative for the population CF patients in a tertiary CF center. Furthermore, the estimated V_D/V_T ratio cannot be accurately predicted from the end-tidal partial pressure of carbon dioxide in patients with an increased V_D/V_T ratio due to lung disease,[42] so caution must be taken with the interpretation of these results.

In conclusion, the OUES seems to be of limited value in children with CF and mild to moderate airflow obstruction as a measure of aerobic exercise capacity derived from submaximal exercise data. This is attributable to its limited ability to distinguish between children with mild to moderate CF and healthy peers, together with its nonlinearity during the last part of CPET and its moderate correlations with $V_{O_{2peak}}$ and the VT.

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Part 2

The steep ramp test

The large van that was used to investigate the reliability and the validity of the steep ramp test, as well as to collect norm values for steep ramp test performance at various schools: the van was equipped with a cycle ergometer and a metabolic cart in order to complete all measurements.

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Medicine and Science in Sports and Exercise
2013;45:366-71

The steep ramp test in healthy children and adolescents

Reliability and validity

Abstract

Background

This study aimed to examine the reliability and validity of the steep ramp test (SRT), a feasible, maximal exercise test on a cycle ergometer that does not require the use of respiratory gas analysis, in healthy children and adolescents.

Methods

Seventy-five children were randomly divided in a reliability group (*n*=37, 17 boys and 20 girls, mean ± SD age: 13.86 ± 3.22 years), which performed two SRTs within two weeks, and a validity group (*n*=38, 17 boys and 21 girls, mean ± SD age: 13.85 ± 3.20 years), which performed both an SRT and regular cardiopulmonary exercise testing (CPET) with respiratory gas analysis within two weeks. Peak work rate (WR_{peak}) was the main outcome of the SRT. Peak oxygen uptake (VO_{2peak}) was the main outcome of CPET. Reliability was examined using the intraclass correlation coefficient and a Bland-Altman plot, whereas validity was assessed using Pearson correlation coefficients and stepwise linear regression analysis.

Results

Reliability statistics for the WR_{peak} values attained at the two SRTs showed an intraclass correlation coefficient of 0.986 (P<0.001). The average difference between the two SRTs was -6.4 W, with limits of agreement between +24.5 and -37.5 W. A high correlation between WR_{peak} attained at the SRT and the VO_{2peak} achieved during CPET was found (r=0.958; P<0.001). Stepwise linear regression analysis provided the following prediction equation:

VO_{2peak} (mL·min^{-1}) = (8.262 × WR_{peak} SRT) + 177.096
(R^2=0.917, standard error of the estimate [SEE]=237.4).

Compared to CPET, significantly lower values at the SRT were found in de validity group for the attained peak heart rate (181 ± 10 versus 193 ± 9 beats·min^{-1}; P<0.001) and the achieved peak minute ventilation (80.7 ± 30.2 versus 93.3 ± 30.7 L·min^{-1}; P<0.001).

Conclusion

The results suggest that the SRT is a reliable and valid exercise test in healthy children and adolescents, which can be used to predict VO_{2peak} and is cardiopulmonary less demanding than regular CPET.

Introduction

Aerobic exercise capacity is an important determinant of overall health, in which a higher aerobic exercise capacity has been related to a lower morbidity and mortality.[1,2] Direct measurement of aerobic exercise capacity during symptom-limited maximal cardiopulmonary exercise testing (CPET) facilitates an accurate and objective assessment of the integrative response of the metabolic, cardiovascular, and pulmonary system to exercise. The results of CPET represent the profiles and adequacy of the physiological responses to exercise, which provide clinically diagnostic and prognostic information.[3] Measuring maximal oxygen uptake ($V\dot{O}_{2max}$) using respiratory gas analysis during incremental exercise is considered to be the gold standard for aerobic exercise capacity by the World Health Organization[4] and others.[5,6] The physiological $V\dot{O}_{2max}$ requires the oxygen uptake ($V\dot{O}_2$) to attain a plateau despite a further increase in work rate (WR).[7] This plateau rarely occurs in pediatric populations.[8,9] Therefore, the highest $V\dot{O}_2$ measured during symptom-limited maximal CPET ($V\dot{O}_{2peak}$) is often considered the best measurable indicator of aerobic exercise capacity.[10,11] Nevertheless, the direct measurement of $V\dot{O}_{2peak}$ in clinical settings is sometimes not feasible because of the expense, the need for special equipment for respiratory gas analysis, and the required trained staff.[12-14]

As exercise testing is sometimes underused in daily (clinical) practice,[15,16] there is a need for less demanding alternatives that do not require respiratory gas analysis. This might help to increase the use of clinical exercise testing. Maximal exercise testing with peak work rate (WR_{peak}) as the primary outcome parameter is a much less demanding procedure.[12] WR_{peak} has been indicated as an appropriate alternative measure of $V\dot{O}_{2peak}$ in healthy children,[12] as well as in children and adolescents with juvenile idiopathic arthritis.[13] The steep ramp test (SRT) is a feasible, short-time incremental exercise test up to maximal exertion with the achieved WR_{peak} as the main outcome, entitled 'maximum short-time exercise capacity' (MSEC). The SRT originates from determination and optimization of training WR in adult patients with chronic heart failure,[17-19] and does not require the use of respiratory gas analysis. Hence, the SRT might contribute to an increase of the use of exercise testing in clinical settings.

Despite its potential clinical applicability, the reliability and validity of the SRT in healthy children and adolescents are currently unknown. Information concerning its reliability and validity is required for clinicians and researchers willing to use the SRT to evaluate (changes in) exercise capacity. Therefore, the purpose of the current study was to investigate the reliability and validity of the SRT in healthy

children and adolescents. Reliability was studied examining the test-retest reliability of the SRT, whereas validity was determined investigating the ability of the SRT to predict $V\text{O}_{2peak}$ attained during regular CPET.

Methods

Participants

Healthy children and adolescents were recruited from primary and secondary schools in the Netherlands. The safety and the possible risk of performing maximal exercise for an individual were assessed before inclusion, using a modified physical activity readiness questionnaire, leading to the exclusion of willing participants who answered 'yes' to one or more questions. Three children were excluded because of musculoskeletal disease, one had cardiovascular disease, and two children reported chest pain in the month before exercise testing when performing physical activity.

Eventually, the study population consisted of 75 healthy participants who were randomly divided in a reliability (n=37) and a validity group (n=38), in which randomization was stratified by sex and age. Children between 8 and 19 years of age who were free from cardiovascular, pulmonary, neurological, or musculoskeletal disease were eligible. The study protocol was approved by the institutional review board of the University Medical Center Utrecht, the Netherlands, and written informed consent was obtained from the legal guardians and/or from the children themselves if they were 12 years or older. Participant characteristics of both groups are presented in TABLE 14.

Study design

To assess the reliability of the SRT, the reliability group performed two SRTs within two weeks (mean ± standard deviation [SD] between-visit time: 8.03 ± 5.29 days). The WR_{peak} attained at the first SRT was compared to the WR_{peak} achieved at the second SRT. To assess the validity of the SRT, the validity group performed an SRT at the first visit and symptom-limited maximal CPET including respiratory gas analysis at the second visit (mean ± SD between-visit time: 8.26 ± 4.71 days). Both maximal exercise tests were performed at the same time of the day for a given participant. The reached WR_{peak} at the SRT was compared to the $V\text{O}_{2peak}$ attained during CPET.

Anthropometry

Anthropometric measurements were conducted before exercise testing. Body mass was measured using an electronic scale (Seca 803; Seca, Hamburg, Germany), and body height was measured using a wall-mounted stadiometer (Seca 206; Seca, Hamburg, Germany). Biological maturity was assessed by measuring sitting height to predict the age from peak height velocity.[20] Body mass index (BMI) was calculated as the body mass divided by body height squared (see *CHAPTER 2*). SD scores were calculated for body height for age, body mass for age, and body mass index for age, using Dutch normative values.[21] Body surface area (BSA) was calculated using the equation of Haycock *et al*.,[22] which has been validated in infants, children, and adults (see *CHAPTER 2*). Percent body fat and subsequent fat free mass (FFM) were determined by measuring subcutaneous fat of the biceps, triceps, subscapular, and supra-iliac regions with a Harpenden skinfold caliper.[23] After estimating body density using the equations proposed by Deurenberg *et al*.,[23] a modification of the Siri equation was used to estimate percent body fat.[24]

TABLE 14. Participant characteristics.

	Reliability group *(n=37)*		**Validity group** *(n=38)*		***P*-value**
Sex (boys/girls)	17/20		17/21		
Age (years)	13.9 ± 3.2	[8.1 – 18.9]	13.9 ± 3.2	[8.1 – 18.9]	0.991
Body mass (kg)	52.8 ± 15.0	[30.0 – 97.8]	51.1 ± 15.3	[23.6 – 94.2]	0.630
Body height (m)	1.62 ± 0.16	[1.29 – 1.87]	1.61 ± 0.14	[1.26 – 1.85]	0.809
Age from peak height velocity (years) [a]	0.8 ± 2.5	[-4.0 – 4.0]	0.8 ± 2.4	[-4.0 – 4.0]	0.978
BMI ($kg \cdot m^{-2}$)	19.9 ± 3.2	[15.3 – 28.8]	19.3 ± 3.3	[13.2 – 31.5]	0.463
BSA (m^2) [b]	1.53 ± 0.28	[1.07 – 2.27]	1.50 ± 0.29	[0.90 – 2.16]	0.630
Body fat (%) [c]	21.0 ± 6.1	[10.7 – 35.5]	19.7 ± 4.7	[10.3 – 30.0]	0.288
FFM (kg)	41.5 ± 11.0	[23.7 – 63.1]	40.8 ± 11.3	[21.2 – 68.5]	0.790

Data are presented as mean ± SD, [range].

ABBREVIATIONS: BMI=body mass index; BSA=body surface area; FFM=fat free mass; SD=standard deviation; [a]: calculated using the equation of Mirwald *et al*.[20]; [b]: calculated using the equation of Haycock *et al*.[22]; [c]: calculated using the equations of Deurenberg *et al*.[23] and Weststrate and Deurenberg.[24]

Exercise testing

Exercise tests were performed on an electronically braked cycle ergometer (Lode Corival; Lode BV, Groningen, the Netherlands) using the Lode Ergometry Manager software (Lode BV, Groningen, the Netherlands). Seat height was adjusted to the participant's leg length. During the tests, heart rate (HR) was monitored by using an elastic belt with an HR sensor (Polar T31i transmitter; Polar, Kempele, Finland). To examine validity, the participants in the validity group breathed through a facemask (Hans Rudolph, Kansas City, MO, USA) during the SRT and CPET, which was connected to a mobile respiratory gas analysis system (Cortex Metamax B[3]; Cortex Medical GmbH, Leipzig, Germany). The metabolic test system was calibrated for respiratory gas analysis measurements (ambient air and a gas mixture of 17% oxygen and 5% carbon dioxide) and volume measurements (3-L syringe) twice a day: in the morning and at noon. The metabolic test system consisted of the facemask and a transmitting unit with oxygen and carbon dioxide analyzers carried on the participant's chest (total weight: 0.57 kg). The mobile respiratory gas analysis system had a wireless connection with a computer, so real-time physical strain of the children during the SRT and CPET could be measured, as indicated by the minute ventilation (V_E), V_{O_2}, carbon dioxide production (V_{CO_2}), and HR averaged at ten-second intervals. This metabolic test system was found to be a reliable and valid system for measuring ventilatory parameters during exercise.[25-27] WR_{peak} was defined as the highest achieved WR, whereas peak V_E ($V_{E_{peak}}$), $V_{O_{2peak}}$, and peak HR (HR_{peak}) were defined as the highest value achieved during the last 30 seconds before peak exercise. Before and directly after the exercise tests, participants completed a ten-point visual analog scale (VAS) indicating their level of fatigue. By doing this, the exhaustiveness of the SRT and CPET (ΔVAS; posttest VAS score minus pretest VAS score) was assessed.

Steep ramp test

To make the test suitable for pediatric populations, the original SRT protocol (WR increments of 25 W·10 s^{-1})[17] was modified. After a three-minute warm-up at 25 W, the test started by applying resistance to the ergometer with increments of 10, 15, or 20 W·10 s^{-1} in a ramp-like manner (2, 3, or 4 W·2 s^{-1}), depending on the participant's body height (<125 cm, between 125 and 150 cm, and >150 cm, respectively; see *CHAPTER 1*, TABLE 2). The participant was instructed to maintain a pedaling frequency between 60 and 80 revolutions·min^{-1}, and the protocol continued until there was a sustained drop in the participant's pedaling frequency from 60 revolutions·min^{-1} despite strong verbal encouragement. Peak exercise was defined as the point at which the participant's pedaling frequency definitely dropped to less than

60 revolutions·min^{-1}. Efforts were considered to be maximal when participants showed subjective signs of intense effort (e.g., unsteady biking, sweating, facial flushing, and clear unwillingness to continue despite encouragement).

Cardiopulmonary exercise testing

During CPET, participants started with a three-minute warm-up at 25 W where after the WR was increased by 10, 15, or 20 W·min^{-1} depending on the participant's body height (<125 cm, between 125 and 150 cm, and >150 cm, respectively).[28] Participants had to maintain a pedaling frequency between 60 and 80 revolutions·min^{-1}. Peak exercise was defined as the point at which there was a sustained drop in the participant's pedaling frequency from 60 revolutions·min^{-1} despite strong verbal encouragement. A test was considered to be at or near the maximal level if at least one of the following criteria was met: an HR_{peak} >180 beats·min^{-1} or a respiratory exchange ratio (RER) at peak exercise (RER_{peak}) >1.0.[29]

Statistical analysis

Data analyses were performed using the Statistical Package for the Social Sciences (SPSS version 15.0; SPSS Inc., Chicago, IL, USA). All data were expressed as mean ± SD and [range], and were verified for normality with Shapiro-Wilk tests. Because all variables were normally distributed, paired samples t-tests were completed to determine whether there were significant differences for test duration, exercise variables, and exhaustiveness between the two SRTs performed by the reliability group, and between the SRT and regular CPET executed by the validity group. The two-way mixed intraclass correlation coefficient (ICC) was computed for both WR_{peak} and WR_{peak} normalized for body mass to assess reliability of the SRT. ICC values higher than 0.75 were considered acceptable.[30] To analyze agreement, limits of agreement were calculated for WR_{peak} according to the procedure described by Bland-Altman,[31] using the two WR_{peak} values attained at the two SRTs. To examine the validity of the SRT, the Pearson correlation coefficient was calculated between the attained WR_{peak} at the SRT and the $\dot{V}O_{2peak}$ achieved during CPET. Stepwise linear regression analysis was used to develop an equation to predict $\dot{V}O_{2peak}$ reached during regular CPET with the SRT performance (WR_{peak}). First, univariate regression analyses were completed to determine which demographic and anthropometric variables were the best candidate predictors of $\dot{V}O_{2peak}$ achieved during CPET. On the basis of their goodness of fit, variables were then selected to be included into the stepwise linear regression analysis. Statistically significant differences were inferred from *P*-values <0.05.

TABLE 15. SRT results of the reliability group.

	First SRT (*n*=37)		Second SRT (*n*=37)		*P*-value
Duration (s) [a]	131 ± 42	[63 – 220]	135 ± 44	[70 – 223]	0.020 *
WR_{peak} (W)	277 ± 93	[131 – 456]	284 ± 97	[133 – 468]	0.018 *
WR_{peak} ($W \cdot kg^{-1}$)	5.2 ± 0.8	[3.6 – 6.5]	5.3 ± 0.9	[3.7 – 6.7]	0.038 *
HR_{peak} ($beats \cdot min^{-1}$) [b]	182 ± 10	[163 – 203]	183 ± 10	[166 – 201]	0.659
ΔVAS	5.5 ± 1.9	[0.7 – 9.3]	6.1 ± 1.8	[1.6 – 9.6]	0.053

Data are presented as means ± SD, [range].

ABBREVIATIONS: ΔVAS=visual analog scale difference addressing the participants' level of fatigue (post SRT minus pre SRT); HR_{peak}=peak heart rate; SD=standard deviation; SRT=steep ramp test; WR_{peak}=peak work rate; [a]: duration of the load phase, excluding warming-up and cooldown; [b]: HR_{peak} was not determinable in 1 boy during the second SRT, so in this case *n*=16 for boys; *: *P*<0.05.

Results

The SRTs were well tolerated by all participants of the reliability group, and they all performed the two SRTs at a maximal effort without any complications or adverse effects. They all met signs of the subjective criteria of maximal effort during the two SRTs, and most the participants also showed objective signs of maximal effort at the SRT, as indicated by an HR_{peak} >180 $beats \cdot min^{-1}$ (53%). The participants of the validity group met the subjective criteria of maximal effort at the SRT and during CPET as well, and they all attained an HR_{peak} >180 $beats \cdot min^{-1}$ and/or an RER_{peak} >1.0 during CPET. A plateau in $\dot{V}O_2$ during maximal exercise[32] was observed in 13 children (34%).

The results of the two SRTs performed by the reliability group are shown in TABLE 15. Although the differences in test duration (3.24 s), WR_{peak} (6.41 W), and WR_{peak} normalized for body mass (0.11 $W \cdot kg^{-1}$) between the two SRTs were small and therefore not clinically relevant, significantly higher values were observed during the second SRT. HR_{peak} and exhaustiveness (ΔVAS) were not significantly different between the two SRTs. Reliability statistics of the SRT showed an ICC of 0.986 (95% confidence interval [CI]: 0.973-0.993; *P*<0.001) for WR_{peak} and an ICC of 0.935 (95% CI: 0.878-0.966; *P*<0.001) for WR_{peak} normalized for body mass. The ICC for the attained HR_{peak} at the SRT was 0.676 (95% CI: 0.451-0.821; *P*<0.001). To analyze agreement between the two SRTs, a Bland-Altman plot is depicted in FIGURE 11. The mean bias ± 1.96 SD between the two SRTs was -6.4 ± 30.9 W. Hence, the limits of agreement for WR_{peak} were +24.5 and -37.3 W.

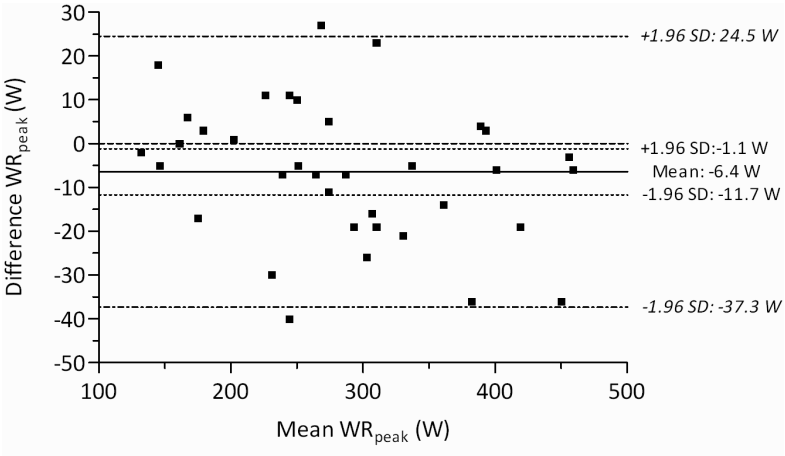

FIGURE 11. Bland-Altman plot of the WR_{peak} as attained at the first SRT versus the second SRT.

ABBREVIATIONS: SD=standard deviation; SRT=steep ramp test; WR_{peak}=peak work rate.

TABLE 16 presents the results of the SRT and CPET completed by the validity group. Although significantly higher values were found for the WR_{peak} attained at the SRT compared to the achieved WR_{peak} during CPET, significantly lower values at the SRT compared to CPET were observed for test duration, HR_{peak}, and V_{Epeak}. All participants of the validity group indicated that they favored the SRT over CPET when they were asked about their preferential maximal exercise test. This is confirmed by the fact that CPET received significantly higher values for exhaustiveness (ΔVAS) than the SRT. FIGURE 12 shows the strong linear relationship between the WR_{peak} attained at the SRT and the V_{O2peak} achieved during CPET. Both variables correlated highly with each other (r=0.958; P<0.001). On the basis of univariate regression analysis, FFM and BSA were also included in the stepwise linear regression analysis. However, the results indicated that WR_{peak} attained at the SRT (P<0.001) remained the only significant predictor of V_{O2peak}, whereas FFM (P=0.377) and BSA (P=0.391) were removed from the model. The following equation was developed to predict V_{O2peak} (mL·min^{-1}) achieved during CPET from the attained WR_{peak} (W) at the SRT:

$$V_{O2peak} = (8.262 \times WR_{peak}\ SRT) + 177.096$$

in which 'V_{O2peak}' represents the predicted peak oxygen uptake in mL·min^{-1} and 'WR_{peak} SRT' is the peak work rate attained at the steep ramp test in W (R^2=0.917, standard error of the estimate [SEE]=237.4).

TABLE 16. SRT and CPET results of the validity group.

	SRT (*n*=38)		CPET (*n*=38)		*P*-value
Duration (s) [a]	139 ± 41	[73 – 232]	558 ± 183	[278 – 949]	<0.001 ***
WR_{peak} (W)	290 ± 94	[138 – 484]	203 ± 69	[94 – 348]	<0.001 ***
WR_{peak} ($W \cdot kg^{-1}$)	5.7 ± 0.7	[4.5 – 7.9]	4.0 ± 0.6	[2.7 – 5.8]	<0.001 ***
HR_{peak} ($beats \cdot min^{-1}$) [b]	181 ± 10	[157 – 201]	193 ± 9	[170 – 209]	<0.001 ***
$\dot{V}E_{peak}$ ($L \cdot min^{-1}$)	80.7 ± 30.2	[27.4 – 170.3]	93.3 ± 30.7	[44.8 – 166.0]	<0.001 ***
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	*NA*	*NA*	50.7 ± 7.8	[36.9 – 71.2]	*NA*
ΔVAS	5.9 ± 1.7	[2.2 – 9.1]	7.2 ± 1.8	[2.3 – 9.9]	<0.001 ***

Data are presented as means ± SD, [range].

ABBREVIATIONS: ΔVAS=visual analog scale difference addressing the participants' level of fatigue (post SRT minus pre SRT and post CPET minus pre CPET); CPET=cardiopulmonary exercise testing; HR_{peak}=peak heart rate; NA=not applicable; SD=standard deviation; SRT=steep ramp test; $\dot{V}E_{peak}$=peak minute ventilation; $\dot{V}O_{2peak}$=peak oxygen uptake; WR_{peak}=peak work rate; [a]: duration of the load phase, excluding warming-up and cooldown; [b]: HR_{peak} was not determinable in 1 girl during both exercise tests, so in this case *n*=20 for girls; ***: *P*<0.001.

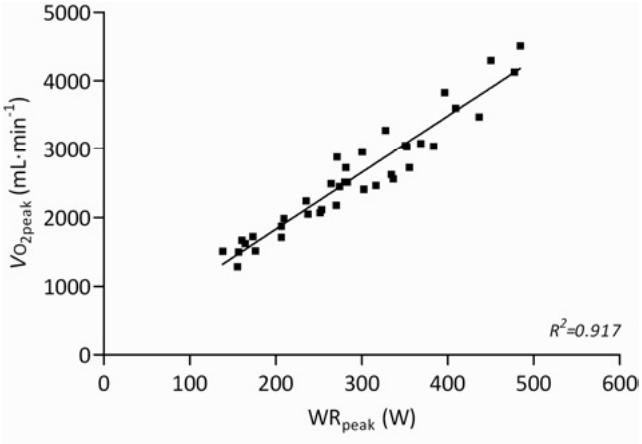

FIGURE 12. The linear relationship between the $\dot{V}O_{2peak}$ attained during CPET and the WR_{peak} attained at the SRT.

ABBREVIATIONS: CPET=cardiopulmonary exercise testing; SRT=steep ramp test; $\dot{V}O_{2peak}$=peak oxygen uptake; WR_{peak}=peak work rate.

Discussion

The aim of this study was to investigate the reliability and the validity of the SRT in healthy children and adolescents. The main results indicate that the SRT comprises good test-retest reliability and is a valid maximal exercise test that can predict $V\dot{O}_{2peak,}$ as reached during regular symptom-limited CPET. In addition, the SRT seems to put a smaller burden on the cardiopulmonary system compared to regular CPET, as shown by the significantly lower values for HR_{peak} and $V\dot{E}_{peak}$ attained during the SRT. The latter is caused by the short duration of the SRT, which in its turn is caused by the fast increase in WR compared to regular CPET. Hence, peripheral muscle strength predominates in limiting SRT performance, with consequential higher WR_{peak} values and lower HR_{peak} and $V\dot{E}_{peak}$ values during the SRT.

Especially in pediatric clinical populations, it is important that an exercise test can be easily performed by the participant. The SRT is a simple, short-time incremental exercise test up to maximal exertion, which was well tolerated by all participants. The current study in healthy children and adolescents demonstrates that the SRT might be appropriate for pediatric clinical populations because of the fact that it does not require respiratory gas analysis, that it has a short duration (approximately between two and three minutes, excluding warm-up and cooldown), that it is reliable, and that it provides a valid equation to predict an individual's $V\dot{O}_{2peak}$.

Regarding its reliability, the average difference between the absolute WR_{peak} values attained at the two SRTs was -6.4 W, indicating that the reliability group on average attained slightly higher WR_{peak} values at the second SRT. Because the differences are scattered symmetrically around the zero-bias line up to 400 W, there is no evidence for a significant learning effect. Very high ICCs (>0.9)[30] were found for both WR_{peak} and WR_{peak} normalized for body mass attained at the SRT. This indicates that the SRT is appropriate to use for discriminative purposes in cross-sectional samples. For clinicians, however, agreement of the measurements is more of interest, as they intend to determine meaningful improvements in a single individual.[33] Concerning agreement, or individual variation between the test and the retest, the average absolute WR_{peak} achieved at the two SRTs showed acceptable limits of agreement (+24.5 to -37.3 W), which means that the agreement as indicated by the smallest detectable change at the SRT equals 30.9 W. Expressed as a percentage, the limits of agreement were 9% to -13% (smallest detectable change: 11%) and appropriate to use in support of evaluative purposes after exercise testing of individuals.

It is difficult to compare the current study outcomes with existing literature because this is, to the authors' knowledge, the first reliability study of the SRT in pediatric participants. De Backer *et al*.[34] investigated the test-retest reliability of the WR_{peak} in adult oncology patients who performed an SRT during cancer rehabilitation, and reported an ICC of 0.996 (95% CI: 0.989-0.998). This is comparable with the ICCs observed in the current study in healthy children and adolescents. Overall, it seems that the SRT performance can be reproducibly performed by healthy children and adolescents.

The WR_{peak} attained at the SRT was highly associated with the $V\dot{O}_{2peak}$ achieved during CPET, showing its validity as a measure of aerobic exercise capacity. The current results are comparable with those of de Backer *et al*.[34] in adult oncology patients, who also observed a significant correlation between the SRT's WR_{peak}, and the $V\dot{O}_{2peak}$ reached during CPET (r=0.82; P<0.01). With the attained WR_{peak} at the SRT, it was therefore possible to predict a child's aerobic exercise capacity. Several other studies predicted aerobic exercise capacity in pediatric populations during exercise testing, including regular CPET,[12,13] and a submaximal treadmill test.[14] $V\dot{O}_{2peak}$ (mL·min^{-1}) could be estimated from the WR_{peak} accomplished during CPET in healthy children (R^2=0.83, SEE=114),[12] as well as in children with juvenile idiopathic arthritis (R^2=0.91, SEE=180).[13] Using a submaximal treadmill test, it was found that $V\dot{O}_{2peak}$ (mL·min^{-1}) could be predicted (based on HR and walking speed among others) in overweight children (R^2=0.75, SEE=271).[14] De Backer *et al*.[34] developed a prediction equation to predict $V\dot{O}_{2peak}$ (mL·min^{-1}) from WR_{peak} attained at the SRT in adult oncology patients and reported an SEE of 308 (R^2=0.67). The current study observed an SEE of 237 when predicting $V\dot{O}_{2peak}$ (mL·min^{-1}), which is comparable with those reported earlier. One can argue that this SEE is larger than those observed by Dencker *et al*.[12] and de Backer *et al*.[13]; however, in these studies, WR_{peak} and $V\dot{O}_{2peak}$ were obtained during the same test. In the current study, the SRT and CPET were both performed approximately eight days apart, which includes also some day-to-day variation in performance (see Reliability section). The same test approach was used by de Backer *et al*.,[34] and the comparison of the results revealed that the current SEE and R^2 values were more favorable than observed in their study. A Bland-Altman plot for the predicted versus the measured $V\dot{O}_{2peak}$ (mL·min^{-1}) in the current study showed a mean difference between the predicted and the measured $V\dot{O}_{2peak}$ of 0.3 mL·min^{-1}, with all values scattered symmetrically around the zero-bias line. The limits of agreement were +459.4 and -458.9 mL·min^{-1}. Nevertheless, the conversion to $V\dot{O}_{2peak}$ might be unnecessary because sex- and age-related reference values for the SRT performance (WR_{peak}) have recently been developed in healthy children and adolescents,[35] which facilitates interpretation of SRT results for clinicians and researchers.

Compared to regular CPET, the significantly lower values for HR_{peak} and $\dot{V}E_{peak}$ indicate that the SRT puts a smaller burden on the cardiopulmonary system as has previously been described in heart failure patients.[18] In relation with this finding, all participants in the validity group indicated that they preferred performing an SRT over CPET. Because exercise testing strongly depends on motivational factors, a more positive affective response during exercise will result in a better adherence to the exercise protocol. Hence, the results of the exercise test will be more reliable and valid.

One of the limitations of this study is that only healthy participants were tested. In future studies, the reliability and validity of the SRT in clinical populations should be investigated. Although the participants' anthropometry differed not significantly from the general Dutch population norms,[21] the currently developed regression equation for the prediction of aerobic exercise capacity by SRT performance should be cross validated in a healthy population, as well as in clinical populations. The lack of habitual physical activity data of the participants and the lack of a randomized testing order within the validity group are additional limitations of the current study.

In conclusion, the SRT seems to be a reliable and valid exercise test, which can predict $\dot{V}O_{2peak}$ in healthy children and adolescents. As the SRT seems to be cardiopulmonary less demanding than regular CPET, it might be of interest for use in clinical populations as well as in less motivated participants.

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Submitted

The steep ramp test in children and adolescents

Age- and sex-related norm values

Abstract

Background

The steep ramp test (SRT) is a feasible, reliable, and valid exercise test on a cycle ergometer that may be more appealing for use in daily (clinical) practice than traditional cardiopulmonary exercise testing. The objective of the current study was to provide sex- and age-related norm values for SRT performance in healthy children and adolescents between the ages of 8 and 19 years.

Methods

Two hundred and fifty-two children and adolescents, 118 boys and 134 girls, performed an SRT (work rate increments of 10, 15, or 20 W·10 s^{-1}, depending on body height) to maximal exertion to assess peak work rate (WR_{peak}). Norm values are presented as reference centiles, developed using generalized additive models for location, scale, and shape.

Results

WR_{peak} correlated highly with age, body mass, body height, body surface area, and fat free mass in boys and girls (r values ranging from 0.811 to 0.930; P<0.001 for all coefficients). The reference curves demonstrated an almost linear increase with age in WR_{peak} in boys, even when normalized for body mass. In contrast, absolute WR_{peak} in girls increased constantly until the age of approximately 13 years, where after WR_{peak} started to level off. WR_{peak} normalized for body mass showed only a slight increase with age in girls, with a slight decrease in relative WR_{peak} as of the age of 14 years.

Conclusion

This study provides sex- and age-related norm values for SRT performance using reference centiles for both absolute and relative WR_{peak}, thereby facilitating the interpretation of SRT results for clinicians and researchers.

Introduction

Physical fitness or aerobic exercise capacity is an important determinant of overall health. Aerobic exercise capacity is typically assessed by measuring peak oxygen uptake ($V\dot{O}_{2peak}$) as an approximate measure of maximal oxygen uptake[1] during maximal cardiopulmonary exercise testing (CPET), the gold standard for assessing $V\dot{O}_{2peak}$. However, standardized exercise testing remains underused in many healthcare centers.[2-4] Moreover, CPET is not feasible in clinical populations where maximal testing is contraindicated or when performance may be impaired by pain, shortness of breath, or fatigue rather than exertion.[5] Thus, a simple, short, inexpensive, reliable, valid, and less physically demanding alternative exercise test may increase the utilization of exercise testing in daily (clinical) practice.

The steep ramp test (SRT) is a short maximal exercise test that does not require respiratory gas analysis measurements. The main outcome of the SRT is the achieved peak work rate (WR_{peak}), which partially reflects anaerobic exercise capacity and leg muscle strength.[6] Performing an SRT may be better tolerated in special populations with chronic disease compared to CPET, since it seemingly places a smaller burden on the cardiopulmonary system. This is due to its short duration, as evidenced by significantly lower values for peak heart rate (HR_{peak}) and peak minute ventilation ($V\dot{E}_{peak}$).[7] An additional advantage of the SRT is the demonstrated strong association between the attained WR_{peak} at the SRT and the $V\dot{O}_{2peak}$ obtained from traditional CPET, as reported in healthy children (r=0.958)[7] and adult cancer survivors (r=0.850).[8] Therefore, the SRT might be useful as a simple screening tool that provides the clinician with an indication about a child's aerobic exercise capacity. With a significantly reduced SRT performance (WR_{peak}), the child can be referred for extensive maximal CPET in order to evaluate the integrated physiological response to exercise precisely.

Although the SRT appears to be a promising alternative to CPET for evaluating aerobic exercise capacity in daily (clinical) practice, there are currently no norm values for the test, which limits the clinician's ability to interpret SRT performance. Therefore, the objective of this study was to provide sex- and age-related norm values for SRT performance in healthy children and adolescents between the ages of 8 and 19 years.

Methods

Participants

In this cross-sectional, observational study, healthy children between 8 and 19 years were recruited from primary and secondary schools throughout the Netherlands, in order to perform a single SRT up to maximal exertion. Written informed consent was obtained from the parents and/or guardians; if the participant was older than 12 years of age, they too were asked to provide written consent. Children suffering from cardiovascular, pulmonary, neurological, or musculoskeletal disease were excluded. All participants completed a modified physical activity readiness questionnaire (PAR-Q) prior to participation to ensure safety. Those answering 'yes' to one or more questions of the modified PAR-Q were also excluded. The study was approved by the medical ethics committee of the University Medical Center Utrecht.

Anthropometry

Prior to exercise testing, body mass (determined to the nearest 0.1 kg) and body height (determined to the nearest 0.5 cm) were measured using an electronic scale (Seca 803; Seca, Hamburg, Germany), and a body meter measuring tape with wall stop (Seca 206; Seca, Hamburg, Germany), respectively. Sitting height was also measured and used to predict the age from peak height velocity as a marker of biological maturity.[9] Body mass index (BMI; $kg \cdot m^{-2}$) was calculated as the body mass divided by body height squared (see *CHAPTER 2*). Standard deviation (SD) scores were calculated for body height for age, body mass for age, and BMI for age, using Dutch normative values.[10] The Haycock *et al*.[11] equation was used to estimate body surface area (BSA; m^2) (see *CHAPTER 2*). Subcutaneous fat distribution was measured using a Harpenden skin fold caliper at four sites on the right side of the body: triceps, biceps, subscapular, and supra-iliacal.[12] The sum of the four skin folds (mm) was used to estimate the body density according to standard equations.[12] Percentage body fat and subsequent fat free mass (FFM; kg) were estimated using a modification of the Siri equation proposed by Weststrate & Deurenberg.[13]

Accelerometry

To assess habitual physical activity (PA), all participants were asked to wear an accelerometer on their right hip for seven consecutive days during all waking

hours, except when engaging in water activities. For practical purposes, two different types of accelerometers were used: the ActiGraph GT3X (Actigraph LLC, Pensacola, FL, USA) and the Actical (Minimitter/Respironics, Bend, OR, USA). Activity was recorded in fifteen-second epochs on both devices. Compliant participants were defined as those who wore the accelerometer for a minimum of four days (including one weekend day) for at least 600 min·day^{-1}. Average wear time (min·day^{-1}), time spent sedentary (min·day^{-1}), time spent in light PA (min·day^{-1}), moderate PA (min·day^{-1}), vigorous PA (min·day^{-1}), moderate-to-vigorous PA (min·day^{-1}), and total PA (min·day^{-1}) were determined based on the count cut points defined by Evenson *et al*.[14]

Steep ramp test

The SRT was performed on an electronically braked cycle ergometer (Lode Corival, Lode BV, Groningen, the Netherlands) using the Lode Ergometry Manager software (Lode BV, Groningen, the Netherlands). Seat height was adjusted to a comfortable leg length for each participant. A modified SRT protocol was used.[7] After a three-minute warming-up phase at 25 W, the test began with the application of a resistance of 10, 15, or 20 W·10 s^{-1} in a ramp-like manner (2, 3, or 4 W·2 s^{-1}), based on the participant's body height (<125 cm, between 125 and 150 cm, and >150 cm respectively; see *CHAPTER 1*, TABLE 2). The participant was instructed to maintain a pedaling rate between 60 and 80 revolutions·min^{-1}. The test was terminated when the participant could no longer maintain the minimum required pedaling rate of 60 revolutions·min^{-1}, despite strong verbal encouragement. Heart rate (HR; beats·min^{-1}) was monitored throughout the test (Polar T31™ transmitter; Polar, Kempele, Finland). WR_{peak} was defined as the work rate (WR; W) at peak exercise, the point at which the participant's pedaling frequency definitely dropped below 60 revolutions·min^{-1}. HR_{peak} was defined as the highest value achieved during the last 30 seconds before test termination. Prior to and directly after the SRT, participants completed a ten-point visual analog scale (VAS) indicating their level of fatigue, allowing the investigators to gain a better understanding of the exhaustiveness of the SRT (ΔVAS; posttest VAS score minus pretest VAS score).

Statistical analysis

Data analyses were performed using the Statistical Package for the Social Sciences (SPSS version 15.0; SPSS Inc., Chicago, IL, USA). All data are expressed as mean ± SD and [range]. Tests for normality were performed on the SRT data using Kolmogorov-Smirnov tests. Differences between boys and girls were examined using independent samples t-tests. A two-way independent analysis of variance

(ANOVA) was used to identify significant differences in the WR_{peak} achieved during the SRT between boys and girls within the different age-groups. Independent samples t-tests were then performed to locate the exact significant differences between boys and girls. Pearson correlation coefficients were calculated to examine associations between the WR_{peak} attained at the SRT and different anthropometric variables. Reference curves were computed as follows: eight models were fitted including all combinations of the two main outcomes of the SRT (WR_{peak} and WR_{peak} normalized for body mass), two predictors (age and body mass) and sex. The outcome distributions were fitted as smooth functions of the predictors through the least mean square (LMS) model using cubic splines.[15] The parameters were estimated by generalized additive models for location, scale, and shape (GAMLSS 4.1-2),[16] and the degree of smoothing needed was chosen by means of the worm plot with nine panels.[17] Computations were performed using the open source statistical package R (version 2.14.2; R Foundation for Statistical Computing, Vienna, Austria). A *P*-value <0.05 was considered statistically significant.

TABLE 17. Participant characteristics.

	Boys *(n=118)*		**Girls** *(n=134)*		***P*-value**	**95% CI**
Age (years)	13.4 ± 3.0	[8.1 – 19.0]	13.4 ± 2.9	[8.2 – 19.0]	0.879	-0.67 – 0.79
Body mass (kg)	51.6 ± 15.6	[23.6 – 104.2]	50.6 ± 13.8	[21.5 – 97.8]	0.563	-2.57 – 4.71
Body height (m)	1.61 ± 0.15	[1.26 – 1.91]	1.58 ± 0.12	[1.23 – 1.87]	0.099	-0.01 – 0.06
Age from peak height velocity (years) [a]	-0.4 ± 2.4	[-4.0 – 4.0]	1.1 ± 2.1	[-3.4 – 4.0]	<0.001 ***	-2.04 – -0.91
BMI ($kg \cdot m^{-2}$)	19.4 ± 3.1	[13.4 – 31.5]	19.8 ± 3.3	[13.2 – 29.4]	0.318	-1.20 – 0.39
BSA (m^2) [b]	1.51 ± 0.29	[0.90 – 2.32]	1.48 ± 0.26	[0.85 – 2.27]	0.436	-0.04 – 0.10
Body fat (%) [c]	17.6 ± 4.9	[9.9 – 30.7]	22.8 ± 4.8	[13.7 – 35.5]	<0.001 ***	-6.40 – -3.98
FFM (kg)	42.3 ± 11.9	[21.2 – 74.0]	38.7 ± 9.3	[17.3 – 63.1]	0.009 **	0.92 – 6.29

Data are presented as mean ± SD, [range].

ABBREVIATIONS: BMI=body mass index; BSA=body surface area; CI=confidence interval; FFM=fat free mass; SD=standard deviation; [a]: calculated using the equation of Mirwald *et al*.[9]; [b]: calculated using the equation of Haycock *et al*.[11]; [c]: calculated using the equations of Deurenberg *et al*.[12] and Weststrate and Deurenberg[13]; ** *P*<0.01; *** *P*<0.001.

TABLE 18. Habitual physical activity of the participants.

	Boys (*n*=118)		Girls (*n*=134)		*P*-value
Wear time (min·day^{-1}) [a, b]	790 ± 42	[712 – 891]	768 ± 43	[664 – 859]	0.001 **
Sedentary time (min·day^{-1}) [a, b]	532 ± 77	[325 – 680]	538 ± 62	[399 – 644]	*NS*
Total PA (min·day^{-1}) [a, b, c]	258 ± 72	[136 – 456]	231 ± 52	[126 – 373]	0.004 **
Light PA (min·day^{-1}) [a, b]	211 ± 56	[110 – 380]	196 ± 44	[91 – 321]	*NS*
Moderate PA (min·day^{-1}) [a, b]	26 ± 15	[7 – 72]	18 ± 9	[4 – 42]	<0.001 ***
Vigorous PA (min·day^{-1}) [a, b]	21 ± 13	[1 – 73]	16 ± 10	[1 – 43]	0.008 **
Moderate-to-vigorous PA (min·day^{-1}) [a, b]	47 ± 21	[12 – 103]	34 ± 15	[10 – 75]	<0.001 ***

Data are presented as mean ± SD, [range].

ABBREVIATIONS: PA=physical activity; SD=standard deviation; [a]: calculated using the count cut points of Evenson *et al.*[14]; [b]: accelerometer wear time was not valid in 35 boys and 38 girls, so in this case *n*=83 in boys and *n*=96 in girls; [c]: total PA represents the sum of light PA, moderate PA, and vigorous PA; **: *P*<0.01; ***: *P*<0.001.

Results

Of the initial 266 participants who were willing to participate and gave written informed consent, 252 were tested (118 boys and 134 girls; age 13.4 ± 2.9 years, range 8-19 years). Five children were excluded due to musculoskeletal disease, two children had neurological disease, two children had cardiovascular disease, three children felt pain in their chest in the month prior to exercise testing when performing physical activity, and two children were not tested due to scheduling issues.

All participants performed a maximal SRT without any complications or adverse events. They all showed subjective signs of maximal effort, including unsteady biking, sweating, facial flushing, and clear unwillingness to continue despite strong verbal encouragement. The majority of the participants (*n*=191) also showed objective signs of maximal effort, as indicated by an HR_{peak} >180 beats·min^{-1}. Participant characteristics are presented in TABLE 17. Compared to girls, boys were significantly less biologically mature, and presented with significantly lower percentage body fat and higher FFM. TABLE 18 shows the habitual PA of the participants. Boys demonstrated higher levels of total PA, which may be explained by more time spent in moderate-to-vigorous PA and vigorous PA than girls.

TABLE 19. SRT results.

	Boys *(n=118)*		Girls *(n=134)*		*P*-value	95% CI
Duration (s)	140 ± 44	[61 – 239]	120 ± 28	[63 – 193]	<0.001 ***	11.0 – 29.5
WR_{peak} (W)	290 ± 100	[126 – 502]	252 ± 67	[120 – 409]	0.001 **	16.3 – 59.2
WR_{peak} ($W \cdot kg^{-1}$)	5.6 ± 0.9	[3.1 – 7.9]	5.0 ± 0.7	[3.4 – 6.6]	<0.001 ***	0.35 – 0.75
HR_{peak} ($beats \cdot min^{-1}$) [a]	185 ± 9	[162 – 203]	186 ± 9	[165 – 210]	0.679	-2.75 – 1.79
ΔVAS	5.9 ± 1.6	[1.5 – 9.3]	5.2 ± 2.0	[0.7 – 9.6]	0.003 **	0.23 – 1.12

Data are presented as mean ± SD, [range].

ABBREVIATIONS: ΔVAS=visual analog scale difference addressing the participants' level of fatigue (post SRT minus pre SRT); CI=confidence interval; HR_{peak}=peak heart rate; SD=standard deviation; SRT=steep ramp test; WR_{peak}=peak work rate; [a]: HR_{peak} was not determinable in 1 boy and 2 girls, so in this case *n*=117 for boys and *n*=132 for girls; **: *P*<0.01; ***: *P*<0.001.

All exercise variables were normally distributed and are presented in TABLE 19. The mean duration of the SRT (excluding warming-up) was 129 ± 38 seconds. Compared to girls, boys cycled significantly longer, resulting in significantly higher values for WR_{peak}. WR_{peak} normalized for body mass was also significantly higher in boys. Boys experienced the SRT as being more exhaustive, as indicated by the higher difference between the pre- and post-test level of fatigue (ΔVAS); however, HR_{peak} was not significantly different between boys and girls.

High correlations were observed between the WR_{peak} and various anthropometric variables, as shown in TABLE 20 for boys and girls separately. As expected, WR_{peak} was positively associated with age, body mass, body height, biological maturity, BSA, and FFM (r values ranging from 0.811 to 0.930; with *P*<0.001 for all coefficients). Moderate positive correlations were found between WR_{peak} and BMI; conversely, no correlation was found between WR_{peak} and percentage body fat.

TABLE 20. Pearson correlation coefficients between WR_{peak} and anthropometric variables.

	Boys *(n=118)*	**Girls** *(n=134)*
Age (years)	r=0.915 *P*<0.001 ***	r=0.811 *P*<0.001 ***
Body mass (kg)	r=0.870 *P*<0.001 ***	r=0.850 *P*<0.001 ***
Body height (m)	r=0.922 *P*<0.001 ***	r=0.896 *P*<0.001 ***
Age from peak height velocity (years)	r=0.949 *P*<0.001 ***	r=0.879 *P*<0.001 ***
BMI ($kg \cdot m^{-2}$)	r=0.564 *P*<0.001 ***	r=0.601 *P*<0.001 ***
BSA (m^2)	r=0.906 *P*<0.001 ***	r=0.885 *P*<0.001 ***
Body fat (%)	r=-0.019 *NS*	r=0.211 *P*=0.014 *
FFM (kg)	r=0.930 *P*<0.001 ***	r=0.902 *P*<0.001 ***

ABBREVIATIONS: BMI=body mass index; BSA=body surface area; FFM=fat free mass; NS=not significant; WR_{peak}=peak work rate; *: *P*<0.05; ***: *P*<0.001.

FIGURE 13 represents the age-related reference centile charts for absolute WR_{peak} for boys and girls at the SRT (upper graphs). The values demonstrate an almost linear increase in WR_{peak} with chronological age; however, commencing at an age of 13 to 14 years, WR_{peak} began to level-off in girls, while WR_{peak} continued to increase linearly in boys. When normalized for body mass, age-related centile charts for WR_{peak} (FIGURE 13, lower graphs) showed an almost linear increase with chronological age up to 19 years old in boys. Girls only demonstrated a slight increase in WR_{peak} normalized for body mass with chronological age, developing into a slight decrease by the age of 14 years. When modeled against body mass (FIGURE 14), the same trends in the study outcomes were found. Of special interest are the distributions of WR_{peak} normalized for body mass as a function of body mass (FIGURE 14, lower graphs). For boys, peak performance occurred around a body mass of 60 kg, whereas in girls, the WR_{peak} normalized for body mass rapidly declined beyond a body mass of approximately 55 kg. As shown in FIGURE 15, boys attained significantly higher absolute WR_{peak} values than girls by the age of 14 years and beyond (upper graph). For the WR_{peak} normalized for body mass (lower graph), there seemed to be a trend towards higher values achieved by boys than girls between the ages of 11 years (*P*=0.015) and 15 years of age. Beyond this age the difference between boys and girls became significant.

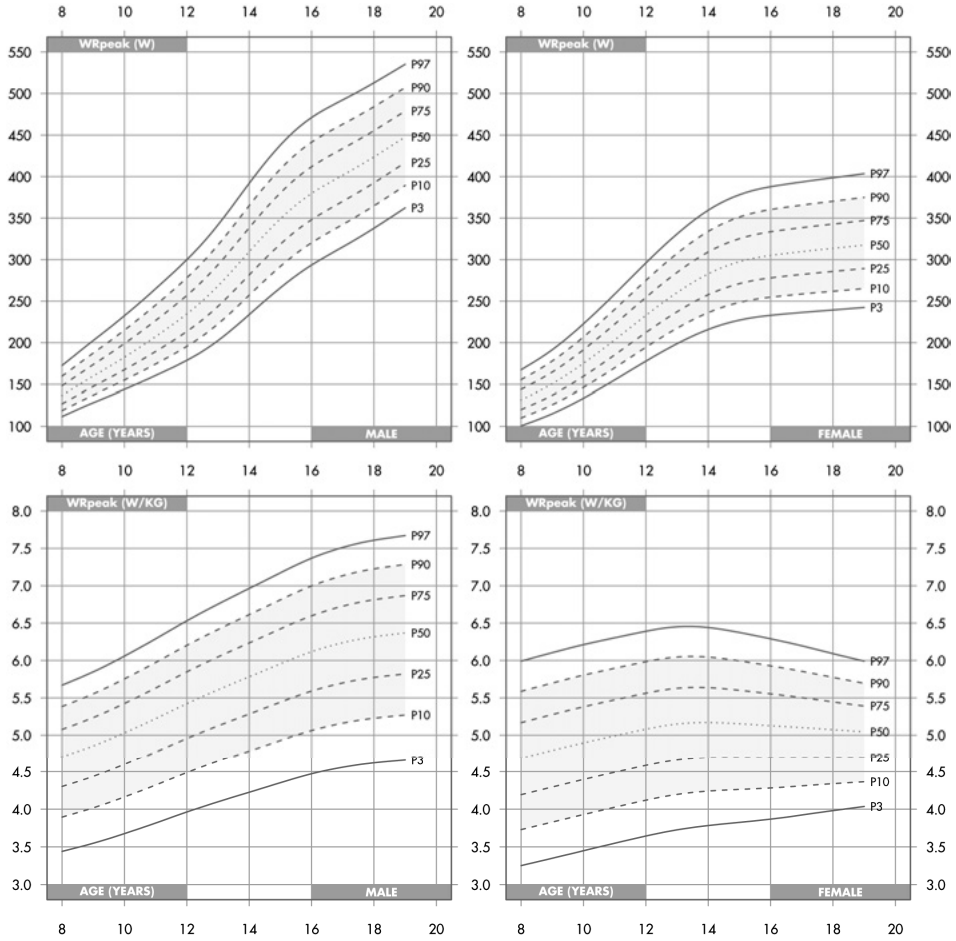

FIGURE 13. Age-related centile charts for the absolute WR_{peak} (upper graphs) and WR_{peak} normalized for body mass (lower graphs) attained at the SRT, for boys and girls separately.

ABBREVIATIONS: SRT=steep ramp test; WR_{peak}=peak work rate.

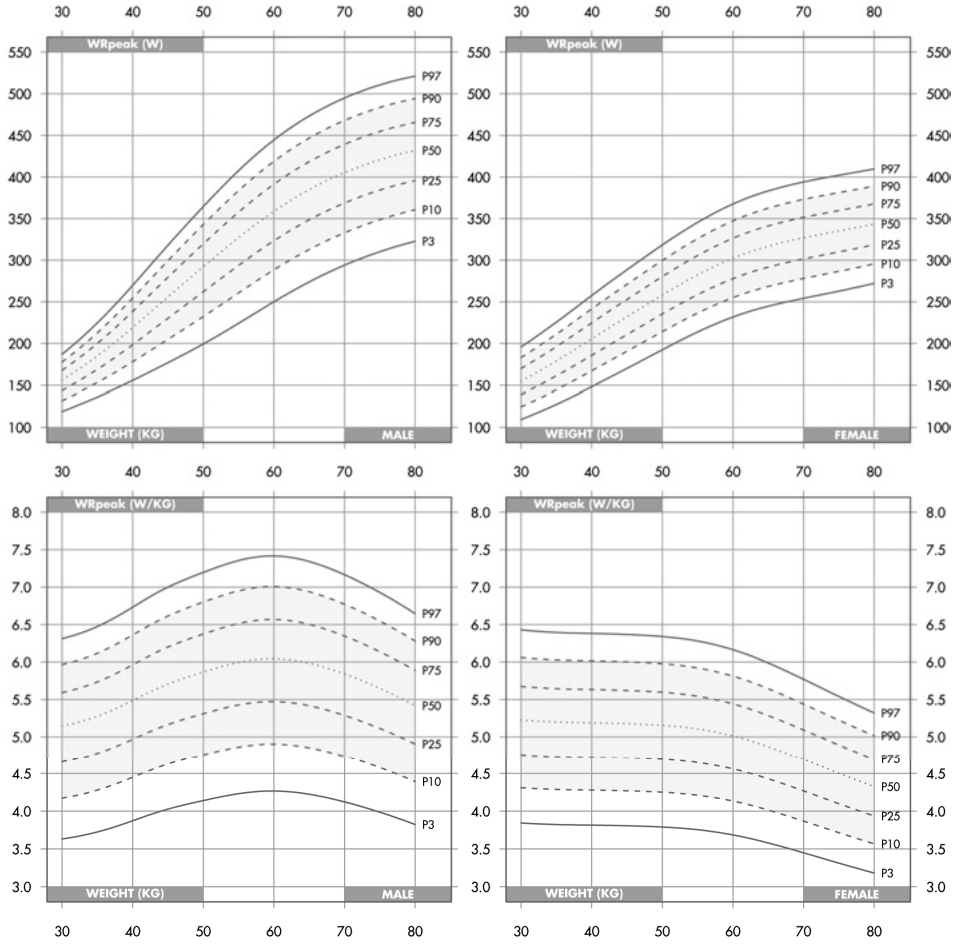

FIGURE 14. Body mass-related centile charts for the absolute WR_{peak} (upper graphs) and WR_{peak} normalized for body mass (lower graphs) attained at the SRT for boys and girls separately.

ABBREVIATIONS: SRT=steep ramp test; WR_{peak}=peak work rate.

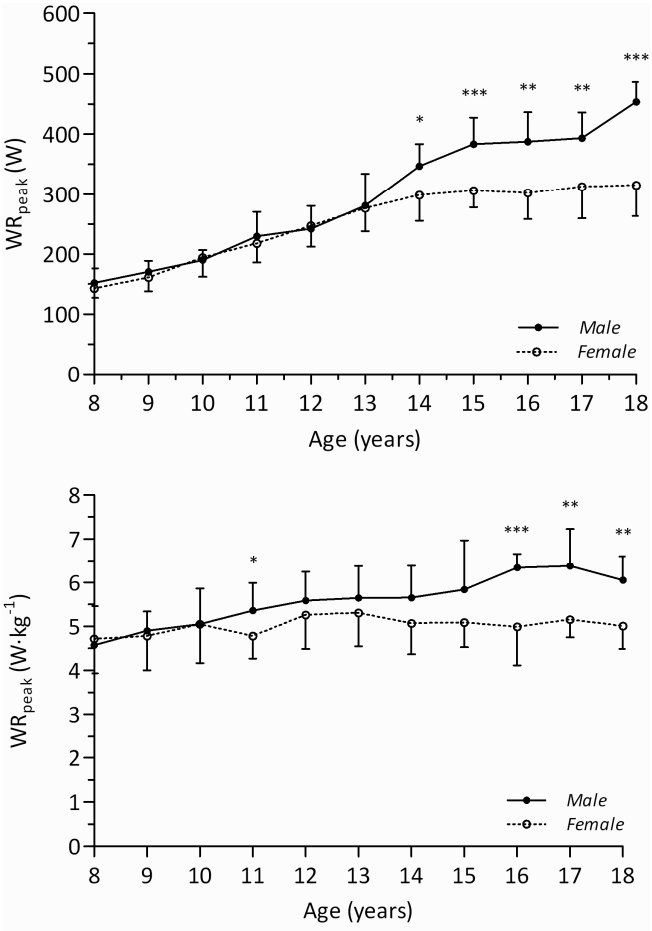

FIGURE 15. Age-related sex differences for the absolute WR_{peak} (upper graph) and WR_{peak} normalized for body mass (lower graph) attained at the SRT.

Data are presented as mean ± SD.

ABBREVIATIONS: SD=standard deviation; SRT=steep ramp test; WR_{peak}=peak work rate; *: *P*<0.05; **: *P*<0.01; ***: *P*<0.001.

Discussion

The objective of the current study was to provide sex- and age-related norm values for the attained WR_{peak} when performing the SRT, in healthy children between 8 and 19 years of age. The SRT was originally developed and described as an alternative measure for determining and readjusting training work rate in adult patients with chronic heart failure.[6,18] Since then, it has been applied in the rehabilitation setting, specifically for prescribing training load and monitoring training progress, of various adult patient groups including oncology patients,[8] patients with chronic obstructive pulmonary disease,[19] type 2 diabetes,[20] and chronic heart failure.[21] The SRT possesses a number of advantageous characteristics compared to performing regular CPET in daily (clinical) practice. First, the test duration is relatively short, two to three minutes excluding warming-up, compared to CPET, which lasts anywhere from eight to twelve minutes excluding warming-up. Second, the SRT does not require expensive respiratory gas analysis measurements. In most (clinical) practice settings, health care professionals do not have access to a metabolic cart. In addition, the use of a facemask or mouthpiece might frighten (young) children.[22] Third, the SRT is known to be a reliable maximal exercise test, which seems to place a much smaller burden on the cardiopulmonary system compared to traditional CPET.[7] The significantly lower reached HR_{peak} and $\dot{V}E_{peak}$ values compared to CPET suggests that local muscle fatigue limits performance on the SRT. Nevertheless, Bongers *et al*.[7] reported high correlation coefficients between the attained WR_{peak} at the SRT and the $\dot{V}O_{2peak}$ achieved during regular CPET (r=0.958; P<0.001). They developed a prediction model that estimates $\dot{V}O_{2peak}$ from the attained WR_{peak} on the SRT. Perhaps most importantly, Bongers *et al*.[7] also showed that the SRT is safe and easily performed by children. By constructing reference curves with age-related reference centiles for the absolute and relative WR_{peak}, the SRT results now have become easy to interpret for clinicians.

For daily (clinical) practice, the SRT might be valuable as a simple screening tool to give an indication about a child's aerobic exercise capacity. A significantly below-average WR_{peak} at the SRT indicates that the child might have a reduced aerobic exercise capacity compared to healthy peers. Since the SRT should not be used as a substitute for regular CPET, children with a reduced SRT performance should be referred for regular CPET in order to assess the integrative physiological response of the cardiovascular, pulmonary, and musculoskeletal system to progressive exercise up to maximal exertion. As a cut-off point that can be used to indicate

subnormal SRT performance, an absolute and/or relative WR_{peak} that falls below the third percentile of the presented reference curves can be used.

The SRT examines aerobic exercise capacity as well as anaerobic exercise capacity. It is evident that with growth, there is a concomitant increase in aerobic exercise capacity and anaerobic exercise capacity. The current results indicate that boys attained significantly higher absolute WR_{peak} values than girls as of 14 years of age and beyond (FIGURE 15, upper graph). This is in line with several studies that investigated aerobic exercise capacity and anaerobic exercise capacity in boys and girls. Bar-Or & Rowland[23] presented aerobic exercise capacity ($\dot{V}O_{2peak}$) data in relation to chronological age of 3,910 boys and girls between 6 and 18 years old, originating from multiple cross-sectional studies. They reported that $\dot{V}O_{2peak}$ values increase until the age of 17 to 18 years in boys, whereas $\dot{V}O_{2peak}$ values hardly increase beyond 14 years of age in girls. This is confirmed by $\dot{V}O_{2peak}$ norm values based on cross-sectional data in a representative group of Dutch children aged 6 to 18 years.[24] When it comes to the development of anaerobic exercise capacity with age, it is generally seen that girls have lower values compared to boys, in which the difference becomes more apparent at age 14 years and beyond.[23] Van Praagh[25] used data from a study[26] to investigate the absolute cycling peak anaerobic exercise capacity in relation to age in boys and girls, and found that girls began diverging from boys at an age of 13 to 14 years, with significantly lower values reported for girls as of 14 to 15 years of age. The sex-associated variation in aerobic and anaerobic exercise capacity is most likely caused by a greater increase in muscle mass with age in boys as well as by a greater increase in body fat with age in girls. This is largely related to changes in endocrine function throughout puberty,[27] with testosterone playing an important role in the gain of muscle strength in boys.[28] It must also be noted that fiber type distribution and neural adaptation may also be factors in age-associated differences in muscle strength.[29] Grip strength, which was found to be a predictor for overall muscle strength, also demonstrates sex differences, especially post-pubertal, with higher values attained by boys.[30] In the current study, the pre-pubertal sex differences (non-significant, with the exception of 11 years of age) in relative WR_{peak} values are likely associated with the higher proportion of body fat in girls.

One limitation of the current study might be that the sample consisted almost entirely of children of Caucasian ethnicity. Whether these norm values are valid for other ethnic groups remains to be determined. Moreover, body mass for age SD scores were significantly different from Dutch population norms in girls (+0.19 SD; P=0.031), whereas BMI for age SD scores differed significantly from the general population norms in boys and girls (+0.29 SD; P=0.002 and +0.24 SD; P=0.006

respectively).[10] Therefore, the sample may not be entirely representative of the Dutch population. Mean SD scores of height for age did not differ significantly from the Dutch norm values in boys and girls.[10]

In conclusion, the current study provides sex- and age-related norm values for SRT performance using reference centiles for both absolute and relative WR_{peak}. The reference curves demonstrated an almost linear increase with age in WR_{peak} in boys up to 19 years old, even when normalized for body mass. In contrast, WR_{peak} in girls increased constantly until the age of approximately 13 years, where after WR_{peak} started to level off. WR_{peak} normalized for body mass showed only a slight increase with age in girls, with a slight decrease in the relative WR_{peak} commencing at 14 years of age. Given the expensive and technical nature of measuring maximal oxygen uptake, the availability of reference curves for the SRT may ease the interpretation of this clinically useful alternative to traditional CPET.

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Steep ramp test performance in children with cystic fibrosis

Abstract

Background

The steep ramp test (SRT) is a non-sophisticated exercise test on a cycle ergometer that does not require respiratory gas analysis. Therefore, the SRT might be able to increase the utilization of clinical exercise testing and exercise training in patients with cystic fibrosis (CF). The objectives of the current study were to evaluate SRT performance in children and adolescents with CF, as well as to compare the physiological responses to the SRT and regular cardiopulmonary exercise testing (CPET) with each other.

Methods

Forty children and adolescents with CF (17 boys and 23 girls, mean ± standard deviation [SD] age: 14.7 ± 1.7 years, mean ± SD FEV_1: 86 ± 18% of predicted) performed an SRT and regular CPET with respiratory gas analysis in a randomized order. Peak work rate (WR_{peak}), peak heart rate (HR_{peak}), peak minute ventilation ($\dot{V}E_{peak}$), and peak oxygen uptake ($\dot{V}O_{2peak}$) were the main outcome measures.

Results

Children and adolescents with CF attained values for absolute and relative WR_{peak} during the SRT that corresponded respectively to 82 ± 14% and 92 ± 14% of predicted. Nutritional status and degree of airway obstruction did not influence SRT performance. Significantly higher values were attained for WR_{peak} at the SRT compared to CPET (252 ± 69 versus 174 ± 46 W; $P<0.001$), while significantly lower values were achieved for HR_{peak} (168 ± 14 versus 182 ± 12 beats·min^{-1}; $P<0.001$), $\dot{V}E_{peak}$ (59.2 ± 19.5 versus 72.0 ± 20.2 L·min^{-1}; $P=0.006$), and $\dot{V}O_{2peak}$ (36.9 ± 7.5 versus 41.5 ± 7.6 mL·kg^{-1}·min^{-1}; $P=0.008$). A strong correlation between WR_{peak} attained at the SRT and the $\dot{V}O_{2peak}$ achieved during CPET was found ($r=0.822$; $P<0.001$).

Conclusion

Since the SRT was well-tolerated in patients with CF and seems to be cardiopulmonary less demanding than regular CPET, it could potentially be used as a feasible alternative for evaluating exercise capacity in patients with a ventilatory limited exercise capacity, as well as to initiate an individually tailored exercise training program on the cycle ergometer.

Introduction

Many children and adolescents with cystic fibrosis (CF) have a significantly reduced aerobic exercise capacity,[1-4] indicated by reduced peak oxygen uptake ($V\dot{O}_{2peak}$) values attained during maximal cardiopulmonary exercise testing (CPET). The reduced exercise capacity in patients with CF seems to have a multi-factorial cause,[5] in which there appears to be an overall interrelationship between lung function, muscle mass, energy expenditure, (respiratory and peripheral) muscle function and exercise capacity.[6] Two decades ago, Nixon *et al.*[7] reported a significant association between exercise capacity of children and adolescents with CF and survival over eight years. Moreover, exercise capacity has been found to be positively linked to quality of life in CF.[8] In addition, several studies have confirmed that exercise and training have many health benefits for patients with CF; it positively affects the transmembrane potential difference,[9] airway mucus clearance,[10] lung function,[11] and exercise capacity.[12]

Therefore, physical activity and exercise training have become increasingly important and widely accepted as parts of therapy and rehabilitation programs in CF management. Nowadays, performing CPET is recommended for standard CF care and follow-up, since it provides the clinician with important diagnostic, prognostic, evaluative, and functional information.[13,14] Moreover, performing CPET is recommended prior to initiation of any exercise training, not only to monitor disease progression, but also to detect exercise-induced limitations and therefore to provide patients with safe training recommendations.[15] Ideally, exercise training should complement current therapies in CF patient healthcare. In previous reports, however, it has emerged that clinicians lack specific recommendations to instruct their patients appropriately.[15]

Despite its clinical value and the above mentioned recommendations, many Cystic Fibrosis Centers currently do not perform CPET as an assessment tool for therapeutic intervention.[16,17] A recent survey indicated that the majority of Cystic Fibrosis Centers in the United Kingdom do not have the equipment (metabolic cart) to directly measure $V\dot{O}_{2peak}$.[17] Therefore, there is a need for non-sophisticated clinical exercise testing procedures that do not require respiratory gas analysis. This might help to increase the utilization of clinical exercise testing and exercise training in patients with CF.

The steep ramp test (SRT) is a non-sophisticated short-time incremental exercise test up to maximal exertion completed on a cycle ergometer. Since the SRT does

not require the use of respiratory gas analysis measurements, it is a non-cardiopulmonary exercise test. The attained peak work rate (WR_{peak}) is its primary outcome measure. The SRT has recently been found to be a reliable and valid exercise test to predict $V\dot{O}_{2peak}$ in healthy children and adolescents, during which the burden on the cardiopulmonary system was smaller compared to regular CPET.[18] Finally, a strong linear relationship between the WR_{peak} attained during the SRT and the $V\dot{O}_{2peak}$ achieved during regular CPET has been reported.[18,19]

These findings highlight the potential for the SRT to provide information concerning the exercise capacity of children and adolescents with CF. Prior to implementing the SRT in standard medical care, knowledge is required concerning SRT performance in children and adolescents with CF. Moreover, it is important to obtain information about the characteristics of the SRT compared to regular CPET in this patient group. Therefore, the objectives of the current investigation were 1) to evaluate SRT performance in children and adolescents with CF, 2) to compare the physiological response to the SRT in children and adolescents with CF to the response to regular CPET, and 3) to validate the prediction equation to predict $V\dot{O}_{2peak}$ with SRT performance, as established in healthy children and adolescents, in children and adolescents with CF.

Methods

Patients

Children and adolescents with CF between 11 and 18 years of age from the Cystic Fibrosis Center of the Wilhelmina Children's Hospital, University Medical Center Utrecht, participated in the current study. Body mass, body height, lung function, and exercise capacity were measured as part of routine assessment measures during their annual check-up. All patients were free from acute pulmonary or gastrointestinal exacerbation at the time of testing. Since exercise testing is part of standard medical care in this Cystic Fibrosis Center, attaining ethical approval and informed consent were not obliged according to the policy of the medical ethical committee of the University Medical Center Utrecht.

Anthropometric measures

Body mass (kg) and body height (m) were determined using an electronic scale (Seca 203; Seca, Hamburg, Germany) and a stadiometer (Ulmer Stadiometer; Prof.

E. Heinze, Ulm, Germany) respectively. Body mass index (BMI) was calculated as the body mass divided by body height squared (see *CHAPTER 2*). Standard deviation (SD) scores were calculated for height for age, body mass for age, body mass for height, and BMI for age using Dutch normative values.[20] The equation of Haycock *et al*.,[21] validated in infants, children, and adults, was used to obtain the patient's body surface area (BSA) (see *CHAPTER 2*).

Spirometry and plethysmography

Spirometry and plethysmography measurements were performed by qualified lung function technicians of the Cystic Fibrosis Center following bronchodilation with salbutamol (800 μg). Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were obtained from flow volume curves (Masterscreen; Jaeger, Würzburg, Germany). FEV_1 was also expressed as a percentage of FVC (Tiffeneau index). Residual volume (RV) and total lung volume (TLC) were determined in a body plethysmograph (Master Laboratory system; Jaeger, Würzburg, Germany). The RV was expressed as a percentage of TLC (RV/TLC%) as well. The internationally used reference values of Zapletal[22] were used to express lung function values as percentage of predicted values.

Exercise testing

After bronchodilation with salbutamol (800 μg), all patients performed CPET and an SRT on an electronically braked cycle ergometer (Lode Corival; Lode BV, Groningen, the Netherlands). Seat height was adjusted to the child's leg length and both exercise tests were completed in a randomized and counterbalanced manner to control for a potential warming-up effect, with equal numbers of patients performing the tests as either CPET-SRT or SRT-CPET. A ten-minute recovery period was completed between the two exercise tests. After the completed exercise tests, the children were asked which exercise test they preferred. During both tests, heart rate (HR) was determined via a twelve-lead electrocardiogram (Cardioperfect; Accuramed BVBA, Herk-de-Stad, Belgium) and peripheral oxygen saturation (Sp_{O_2}) at the index finger was measured by pulse oximetry (Masimo Rad-8; Masimo Inc., Irvine, CA, USA). Moreover, children breathed through a facemask (Hans Rudolph, Kansas City, MO, USA) during CPET and the SRT, with the purpose to perform breath-by-breath respiratory gas analysis and volume measurements using a respiratory gas analysis system (ZAN 600; Accuramed BVBA, Herk-de-Stad, Belgium). Gas analyzers were calibrated using gases of known concentration, while the flow meter was calibrated using a 3-L syringe (Hans Rudolph, Kansas City, MO, USA). Minute ventilation ($\dot{V}_E$), oxygen uptake ($\dot{V}_{O_2}$), carbon dioxide production

($\dot{V}CO_2$), and respiratory exchange ratio (RER) were calculated from conventional equations. Output from the flow meter and gas analyzers were averaged over ten-second intervals and stored for further use. Peak exercise parameters were defined as the highest values achieved within the last 30 seconds prior to maximal exertion.

Cardiopulmonary exercise testing

Prior to performing CPET, patients rested until all measured variables were stable. During CPET, participants started with three minutes of unloaded cycling, after which the work rate (WR) was increased by 10, 15, or 20 W·min^{-1}, depending on the participant's body height (<125 cm, between 125 and 150 cm, and >150 cm respectively),[23] in a ramp-like manner (2, 3, or 4 W·12 s^{-1}). Patients had to maintain a pedaling frequency between 60 and 80 revolutions·min^{-1}. Peak exercise was defined as the point at which there was a sustained drop in pedaling frequency from 60 revolutions·min^{-1}, despite strong verbal encouragement. A test was considered to be at or near the maximal level if at least one of the following criteria was met: an HR at peak exercise (HR_{peak}) >180 beats·min^{-1} or an RER at peak exercise (RER_{peak}) >1.0.[24] In order to measure the exhaustiveness of CPET, the children's OMNI scale of perceived exertion was used, which has been validated in children.[25] The scale starts with '0', indicating the child is 'not tired at all', and ends with '10', meaning that the child is 'very, very tired'. The patients had to fill out the OMNI-scale before and directly after CPET in order to obtain a ΔOMNI score (post-test OMNI score minus pretest OMNI score). Recently constructed Dutch reference values[26] were used to express the attained WR_{peak} and $\dot{V}O_{2peak}$ during CPET, performed according to the Godfrey protocol,[23] as a percentage of predicted.

Steep Ramp Test

Participants rested until all measured variables were stable. After a three-minute warming-up at 25 W, the SRT started by applying resistance to the ergometer in a ramp-like manner (2, 3, or 4 W·2 s^{-1}), resulting in increments of 10, 15, or 20 W·10 s^{-1} depending on the participant's body height (<125 cm, between 125 and 150 cm, and >150 cm respectively, see *CHAPTER 1*, TABLE 2).[18] The participant was instructed to maintain a pedaling frequency between 60 and 80 revolutions·min^{-1}, and peak exercise was defined as the point at which the pedaling frequency definitely dropped from 60 revolutions·min^{-1}. Efforts were considered to be maximal when participants showed subjective signs of intense effort (e.g. unsteady biking, sweating, facial flushing, and clear unwillingness to continue despite encouragement). Before and directly after the SRT, the participants had to fill out

the children's OMNI scale of perceived exertion in order to measure the exhaustiveness of the SRT (ΔOMNI score). The attained WR_{peak} at the SRT was compared to Dutch norm values[27] and expressed as a percentage of predicted.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS, version 15.0; SPSS Inc., Chicago, IL, USA) was used to analyze the data. Data are presented as mean values ± SD. Shapiro-Wilk tests were performed in order to confirm normal distribution of the data. As appropriate, an independent samples t-test or its non-parametric equivalent, the Mann-Whitney U test, was performed on the anthropometric and the exercise variables to test for significant differences between boys and girls and between the SRT and CPET. Pearson's correlation coefficients were calculated between the attained WR_{peak} at the SRT and several anthropometric, lung function, and exercise variables. A Bland-Altman plot[28] was constructed in order to validate the equation to predict $V\dot{O}_{2peak}$ from SRT performance in children and adolescents with CF. A *P*-value <0.05 was considered statistically significant.

TABLE 21. Participant characteristics.

	Boys *(n=17, 43%)*	**Girls** *(n=23, 57%)*	***P*-value**
Age (years)	15.1 ± 2.1 [11.2 – 18.1]	14.3 ± 1.2 [11.8 – 16.9]	0.198
CF genotype:			
ΔF508/ΔF508 homozygous	*n=9 (53%)*	*n=15 (65%)*	*NA*
ΔF508/Other	*n=7 (41%)*	*n=8 (35%)*	*NA*
Other/Other	*n=1 (6%)*	*n=0 (0%)*	*NA*
Body mass (kg)	51.5 ± 10.3 [36.0 – 70.2]	49.4 ± 8.8 [30.0 – 63.4]	0.493
Body mass for age SD score [a, b]	-0.53 ± 0.57 [-1.39 – 0.51]	-0.38 ± 0.99 [-2.77 – 1.19]	0.485
Body height (m)	1.67 ± 0.14 [1.46 – 1.87]	1.62 ± 0.09 [1.39 – 1.78]	0.211
Body height for age SD score [a, b]	-0.67 ± 0.87 [-1.86 – 0.84]	-0.30 ± 1.07 [-2.80 – 1.69]	0.345
BMI ($kg \cdot m^{-2}$) [b]	18.2 ± 1.3 [16.6 – 20.2]	18.6 ± 1.7 [15.2 – 20.8]	0.411
BMI for age SD score [a]	-0.39 ± 0.65 [-1.44 – 1.10]	-0.21 ± 0.74 [-1.96 – 0.66]	0.405
BSA (m^2) [c]	1.54 ± 0.21 [1.20 – 1.90]	1.48 ± 0.18 [1.07 – 1.76]	0.414

Data are presented as mean ± SD, [range] or as n (%).

ABBREVIATIONS: CF=cystic fibrosis; BMI=body mass index; BSA=body surface area; NA=not applicable; SD=standard deviation; [a]: calculated using Dutch normative values[20]; [b]: Mann-Whitney U test; [c]: calculated using the equation from Haycock *et al*.[21]

Results

Forty-one patients with CF performed both CPET and an SRT at their annual check-up within the study period. Eventually, one 13-year-old boy was excluded from analysis, since he did not meet the subjective and objective criteria of a maximal effort at both exercise tests due to lack of motivation. Participant characteristics of the other 40 patients with CF are listed in TABLE 21, for boys (*n*=17) and girls (*n*=23) separately. There were no significant differences between boys and girls concerning age and anthropometric characteristics. Lung function characteristics are listed in TABLE 22. With a mean FEV_1 of 86 ± 18% of predicted and a RV/TLC% of 28 ± 10%, the total group of children with CF suffered from mild airflow obstruction. Boys attained significantly higher absolute FEV_1 values and significantly lower RV/TLC% values compared to girls.

All 40 patients terminated CPET and the SRT due to voluntary exhaustion, without adverse effects. They all met the subjective criteria of a maximal effort during CPET and the SRT, and all but one patient attained an HR_{peak} >180 beats·min^{-1} and/or an RER_{peak} >1.0 during CPET. The patient that did not meet the latter criteria had an FEV_1 value of 45% of predicted and performed symptom-limited CPET due to dyspnea.

TABLE 22. Lung function characteristics.

	Boys *(n=17, 43%)*		**Girls** *(n=23, 57%)*		***P*-value**
FEV_1 (L)	3.15 ± 1.07	[1.31 – 5.32]	2.52 ± 0.69	[1.33 – 3.91]	0.043 *
% of predicted [a]	*91 ± 18*	*[45 – 118]*	*83 ± 17*	*[51 – 112]*	*0.169*
FVC (L) [b]	3.73 ± 1.00	[2.16 – 5.51]	3.21 ± 0.67	[1.71 – 4.42]	0.083
% of predicted [a, b]	*93 ± 13*	*[62 – 116]*	*90 ± 12*	*[61 – 115]*	*0.406*
Tiffeneau index (%) [b]	80 ± 11	[61 – 99]	79 ± 9	[64 – 93]	0.761
% of predicted [a, b]	*96 ± 13*	*[72 – 117]*	*94 ± 11*	*[76 – 111]*	*0.761*
RV (L) [c, d]	1.24 ± 0.64	[0.35 – 3.03]	1.43 ± 0.40	[0.75 – 2.16]	0.119
TLC (L) [c]	5.04 ± 1.29	[3.13 – 6.95]	4.68 ± 0.79	[2.85 – 6.07]	0.356
RV/TLC% [c, d]	24 ± 11	[11 – 57]	31 ± 8	[17 – 46]	0.011 *

Data are presented as mean ± SD, [range].

ABBREVIATIONS: FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; RV=residual volume; RV/TLC%=ratio of the residual volume to the total lung volume; SD=standard deviation; TLC=total lung capacity; [a]: calculated using reference values from Zapletal[22]; [b]: FVC was not determined in 1 boy and 2 girls, so in this case *n*=16 for boys and *n*=21 for girls; [c]: Body plethysmography was not performed in 2 boys and 4 girls, so in this case *n*=15 for boys and *n*=19 for girls; [d]: Mann-Whitney U test; *: *P*<0.05.

TABLE 23 presents the results of the patients with CF during CPET and the SRT. They attained mean $V\dot{O}_{2peak}$ values during CPET of 93% of predicted. This indicates that overall, the children with CF had an aerobic exercise capacity within the normal range. Compared to Dutch norm values for SRT performance, children and adolescents with CF attained values for absolute (252 ± 60 W) and relative (5.0 ± 0.8 W·kg^{-1}) WR_{peak} during the SRT that corresponded to 82 ± 14% and 92 ± 14% of predicted respectively. Percentage of predicted values for WR_{peak} normalized for body mass were significantly higher than absolute WR_{peak} values, expressed as a percentage of predicted (P<0.001), due to the generally decreased body weight (see TABLE 21). During the SRT, significantly higher values were attained for both absolute and relative WR_{peak} compared to CPET, while significantly lower values at the SRT compared to CPET were achieved for HR_{peak}, peak $V\dot{E}$ ($V\dot{E}_{peak}$), and $V\dot{O}_{2peak}$. The duration of the load phase of the SRT protocol was on average two minutes and ten seconds, which was significantly shorter than the load phase during CPET that lasted for almost nine minutes. All patients with CF indicated that they favored performing an SRT over CPET when they were asked about their preferential maximal exercise test. This is confirmed by the objective fact that the SRT received significantly lower values for exhaustiveness (ΔOMNI) than CPET.

To examine SRT performance in children with CF more detailed, patients were also subdivided based on nutritional status: a group with a BMI for age SD score ≥-1.00 (n=31) and a group with a BMI for age SD score <-1.00 (n=9) (FIGURE 16, upper graph). No differences between both groups were found for age (14.6 ± 1.7 versus 14.9 ± 1.7 years; P=0.636), body height (1.65 ± 0.11 versus 1.64 ± 0.15 m; P=0.873), body mass (51.7 ± 8.7 versus 45.4 ± 10.5 kg; P=0.072), FEV_1 (89 ± 16 versus 79 ± 22% of predicted; P=0.147), and RV/TLC% (26 ± 8 versus 34 ± 14%; P=0.154). FIGURE 16, upper graph, shows that children with CF and a BMI for age SD score ≥-1.00 attained significantly higher values for absolute WR_{peak} at the SRT (85 ± 12 versus 72 ± 16% of predicted), whereas there was no between-group difference when SRT performance was normalized for body mass (91 ± 12 versus 92 ± 19% of predicted). Patients were also divided in subgroups based on the degree of airway obstruction: a mild group (FEV_1 ≥80%, n=26) and a moderate group (FEV_1 <80%, n=14) (FIGURE 16, lower graph). No between-group differences were found for age (14.5 ± 1.7 versus 14.9 ± 1.7 years; P=0.589), body height (1.65 ± 0.13 versus 1.64 ± 0.08 m; P=0.921), body mass (50.5 ± 10.1 versus 50.0 ± 8.2 kg; P=0.898), and BMI (18.3 ± 1.5 versus 18.5 ± 1.6 kg·m^{-2}; P=0.726). The mild group had significantly lower values for the RV/TLC% (24 ± 7 versus 35 ± 11%; P=0.001). There were no between-group differences in the reached absolute (83 ± 15 versus 80 ± 12% of predicted) and relative (92 ± 14 versus 91 ± 14% of predicted) WR_{peak} at the SRT (FIGURE 16, lower graph).

TABLE 23. CPET and SRT results.

	CPET		SRT		Difference	*P*-value
Time (s) [a]	536 ± 124	[315 – 810]	132 ± 27	[75 – 195]	-75%	<0.001 ***
WR_{peak} (W)	174 ± 46	[98 – 270]	252 ± 60	[127 – 385]	+45%	<0.001 ***
% of predicted	*87 ± 16* [b]	*[52 – 118]*	*82 ± 14* [c]	*[44 – 105]*	*-6%*	*0.112*
WR_{peak} ($W \cdot kg^{-1}$)	3.5 ± 0.6	[2.4 – 4.9]	5.0 ± 0.8	[3.5 – 6.5]	+43%	<0.001 ***
% of predicted	*95 ± 15* [b]	*[70 – 127]*	*92 ± 14* [c]	*[67 – 117]*	*-3%*	*0.301*
HR_{peak} ($beats \cdot min^{-1}$)	182 ± 12	[148 – 206]	168 ± 14	[130 – 195]	-8%	<0.001 ***
$\dot{V}E_{peak}$ ($L \cdot min^{-1}$)	72.0 ± 20.2	[33 – 126]	59.2 ± 19.5	[17 – 126]	-18%	0.006 **
Ventilatory reserve (%)	23 ± 20	[-21 – 57]	37 ± 20	[-31 – 75]	+61%	0.005 **
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	41.5 ± 7.6	[23.8 – 52.3]	36.9 ± 7.5	[17.9 – 49.9]	-11%	0.008 **
% of predicted	*93 ± 15* [b]	*[56 – 122]*	*NA*		*NA*	*NA*
SpO_2 drop (%) [d, e]	2.1 ± 2.4	[-2 – 8]	1.3 ± 2.0	[-1 – 7]	-38%	0.113
ΔOMNI [f]	6.7 ± 2.2	[2.0 – 10.0]	5.5 ± 2.3	[0.0 – 9.0]	-18%	0.043 *

Values are presented as mean ± SD, [range].

ABBREVIATIONS: ΔOMNI=posttest OMNI score minus pretest OMNI score; CPET=cardiopulmonary exercise testing; HR_{peak}=peak heart rate; SD=standard deviation; SpO_2=peripheral measured oxygen saturation; SRT=steep ramp test; $\dot{V}E_{peak}$=peak minute ventilation; $\dot{V}O_{2peak}$=peak oxygen uptake; WR_{peak}=peak work rate; [a]: duration of the load phase of the protocol; [b]: calculated using reference values from Bongers *et al.*[26]; [c]: calculated using reference values from Bongers *et al.*[27]; [d]: SpO_2 determination was invalid in 3 boys and 2 girls, so in this case *n*=35; [e]: Mann-Whitney U test; [f]: ΔOMNI was not determined in 2 boys and 6 girls, so in this case *n*=32; *: *P*<0.05; **: *P*<0.01; ***: *P*<0.001.

Furthermore, moderate to strong correlations were found between SRT performance (WR_{peak}) and some anthropometric variables (age: r=0.665, body height: r=0.768, body mass: r=0.746, and BSA: r=0.760; with *P*<0.001 for all coefficients), lung function variables (absolute FEV_1: r=0.675, absolute FVC: r=0.703, and TLC: r=0.669; with *P*<0.001 for all coefficients), and CPET variables (WR_{peak}: r=0.922, $\dot{V}O_{2peak}$: r=0.822, and $\dot{V}E_{peak}$: r=0.763; with P<0.001 for all coefficients). FIGURE 17 depicts the strong linear relationship between the absolute WR_{peak} attained at the SRT and the absolute $\dot{V}O_{2peak}$ achieved during CPET. A strong correlation was also observed between the absolute WR_{peak} achieved at the SRT expressed as a percentage of predicted and the absolute WR_{peak} reached during CPET expressed as a percentage of predicted (r=0.837; *P*<0.001). Between the relative WR_{peak} achieved at the SRT and the relative WR_{peak} attained during CPET, both expressed as a percentage of predicted, a slightly lower correlation coefficient was found (r=0.775; *P*<0.001).

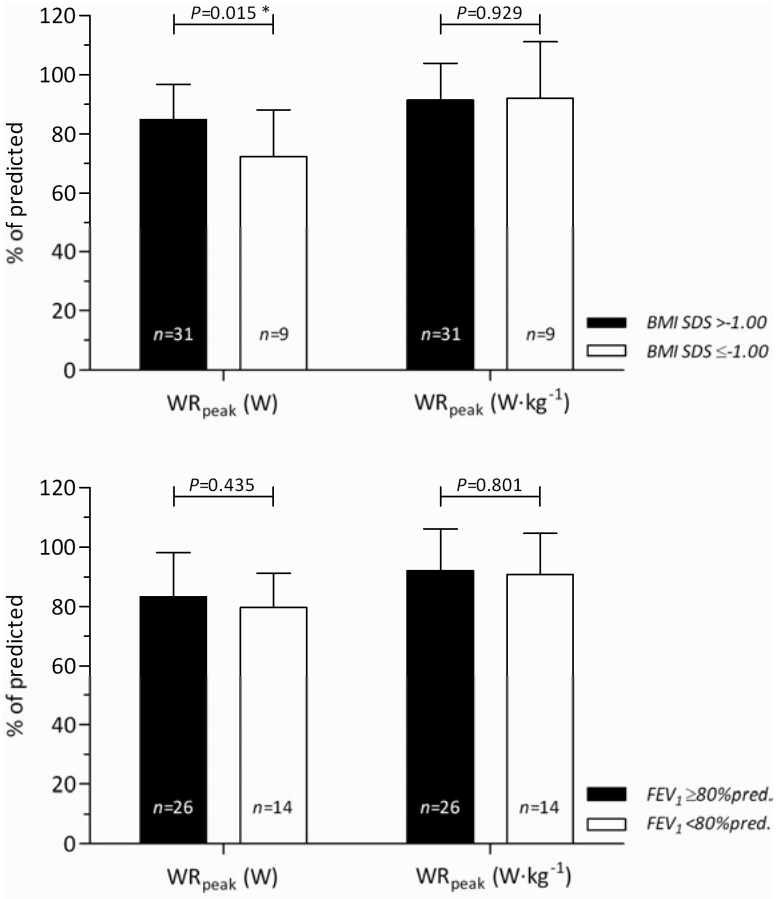

FIGURE 16. Subgroup analyses on SRT performance in children with CF. Subgroups are based on nutritional status (upper graph) and the degree of airway obstruction (lower graph).

Data are presented as mean + SD.

ABBREVIATIONS: BMI=body mass index; CF=cystic fibrosis; FEV_1=forced expiratory volume in one second; SD=standard deviation; SDS=standard deviation score, calculated using Dutch normative values[20]; WR_{peak}=peak work rate.

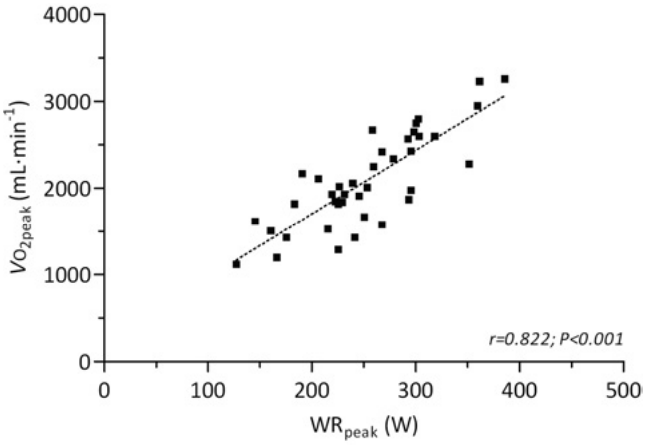

FIGURE 17. The linear relationship between the WR_{peak} attained at the SRT and the VO_{2peak} attained during CPET in children with CF (R^2=0.676).

ABBREVIATIONS: CF=cystic fibrosis; CPET=cardiopulmonary exercise testing; SRT=steep ramp test; VO_{2peak}=peak oxygen uptake; WR_{peak}=peak work rate.

In order to validate the equation established in healthy children and adolescents to predict the VO_{2peak} attained during CPET from SRT performance, the absolute WR_{peak} attained at the SRT by the children with CF was used to predict their VO_{2peak} reached during CPET by the following formula[18]:

$$VO_{2peak} = (8.262 \times WR_{peak}\ SRT) + 177.096$$

in which 'VO_{2peak}' stands for the predicted peak oxygen uptake in mL·min^{-1} and 'WR_{peak} SRT' represents the peak work rate attained at the steep ramp test in W (R^2=0.917, standard error of the estimate [SEE]=237.4). As depicted in FIGURE 18, the Bland-Altman plot demonstrates an average bias ± 1.96 SD between the predicted and the measured VO_{2peak} of -175.4 ± 309.6 mL·min^{-1} in our group of patients with CF. The limits of agreement were +431.4 mL·min^{-1} and -782.1 mL·min^{-1}.

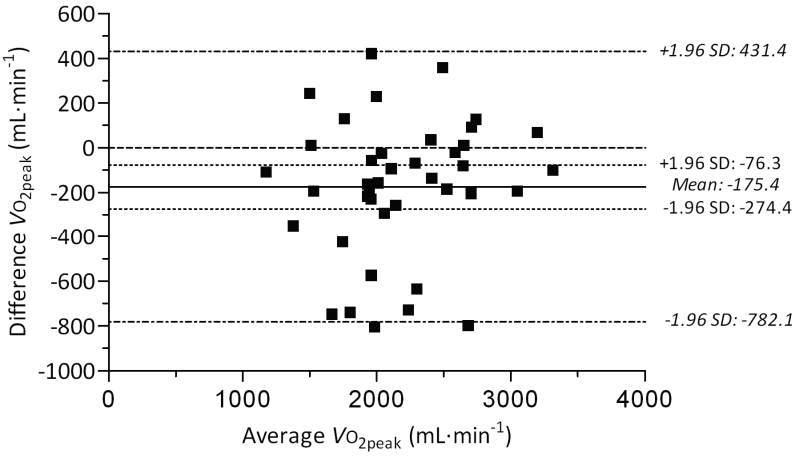

FIGURE 18. Bland-Altman plot of the VO_{2peak} attained during CPET predicted from SRT performance versus the measured VO_{2peak} attained during CPET in children with CF.

ABBREVIATIONS: CF=cystic fibrosis; CPET=cardiopulmonary exercise testing; SD=standard deviation; SRT=steep ramp test; VO_{2peak}=peak oxygen uptake.

Discussion

The current study evaluated SRT performance in children and adolescents with CF and compared the physiological response to the SRT in patients with CF to the response to regular CPET. Moreover, the validity of the prediction equation to predict VO_{2peak} with SRT performance, as established in healthy children and adolescents, in children and adolescents with CF was investigated. The main results indicate that the SRT is a feasible short-time incremental exercise test up to maximal exertion in children and adolescents with CF. They achieved values for absolute and relative WR_{peak} during the SRT corresponding to 82% and 92% of predicted. The WR_{peak} attained at the SRT correlated strongly with the VO_{2peak} achieved during CPET. Perhaps most importantly for this population, it seems that the SRT is cardiopulmonary less demanding compared to regular CPET, since significantly lower HR_{peak}, VE_{peak}, and ΔOMNI values were found, as well as significantly higher values for the ventilatory reserve at peak exercise.

A post hoc analysis was performed in order to examine the effect of nutritional status and the degree of airway obstruction on SRT performance. Results show that nutritional status does not influence SRT performance, since there was no significant difference in the attained WR_{peak} at an equivalent body mass expressed

as a percentage of predicted between the subgroups. Although body mass was found to be a significant predictor of SRT performance, it would be interesting to examine the effect of nutritional status on SRT performance after normalizing for fat free mass (FFM), since normalizing for body mass has been reported to overestimate the work capacity in patients with CF during CPET. 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 body mass.[29] From a physiological perspective, FFM, as an indicator of muscle mass, would be the best indicator for SRT performance. This is confirmed by a study in healthy boys and girls, in which SRT performance was found to be best correlated to FFM (r=0.930 and r=0.902 respectively; with $P<0.001$ for both coefficients).[27]

The degree of airway obstruction was also found to have no influence on SRT performance. There were no significant differences in the attained WR_{peak} at an equivalent body mass between mildly and moderately obstructed patients with CF. However, it is possible that severe airway obstruction does limit SRT performance. Boas *et al*.[30] reported that the degree of airway obstruction was not a significant predictor of anaerobic exercise capacity, as measured during a Wingate anaerobic test (WAnT). The authors explained this by suggesting that anaerobic exercise capacity is dependent on the anaerobic characteristics of the exercising muscles and not on oxygen transport. SRT performance also relies on anaerobic exercise capacity. In fact, with significantly higher WR_{peak} values (+45%) and significantly lower $\dot{V}O_{2peak}$ values (-11%) compared to CPET found in the current study, it is clear that the SRT requires a substantial part of anaerobic glycolysis for energy production. This is in agreement with a recent study[31] that reported lower $\dot{V}O_2$ values at equal WR values at the SRT compared to CPET, and may be explained by the slower $\dot{V}O_2$ on-kinetics observed in steeper ramp slopes which are suggested to compromise the aerobic contribution to total energy delivery.[32] Nevertheless, being independent of lung function highlights the potential of the SRT to be used as a clinical useful alternative for traditional CPET in patient groups with severe airway obstruction.

Due to the relatively large contribution of anaerobic energy utilization during the SRT, this test might also serve to evaluate the effects of a high-intensity interval exercise training (HIT) program. This is also where the SRT originates from. It was introduced in order to determine and optimize HIT work rate in adult patients with chronic heart failure.[33-35] HIT might be an effective and efficient training regimen in children with CF, especially in ventilatory limited patients.[36] Since children's physical activity patterns are characterized by short intense bursts of activity,[37] HIT might be an appropriate method to improve exercise tolerance,

because it involves significant anaerobic energy utilization. Therefore, it is believed to better mimic the physiological requirements of activities of daily living in children.[38]

The equation that was established in healthy children and adolescents to predict $V\dot{O}_{2peak}$ attained during CPET from SRT performance, was found to overestimate the $V\dot{O}_{2peak}$ reached during CPET in children and adolescents with CF. This is probably due to the fact that children and adolescents with CF were found to have slower $V\dot{O}_2$ kinetics.[39,40]

For future research, it would be interesting to examine SRT performance normalized for FFM in children and adolescents with CF, also in subgroups based on nutritional status, lung function, and oxygen saturation level. Therefore, it would also be interesting to examine the exact contribution of the oxidative metabolism and anaerobic glycolysis during the SRT in children with CF compared to healthy peers. Further research is also needed in order to investigate SRT performance in patients with CF and severe airway obstruction. Finally, it would be interesting to study the responsiveness of SRT performance after HIT in children with CF in order to evaluate whether the SRT can be used to determine training intensity and monitor training progress.

In conclusion, the SRT seems to be a time-efficient, low-cost exercise test that does not require respiratory gas analysis, while its primary outcome measure (WR_{peak}) is strongly correlated to $V\dot{O}_{2peak}$ in children and adolescents with CF. As the SRT was well-tolerated by patients with CF, and seems to be cardiopulmonary less demanding than regular CPET, it could potentially be used as a feasible alternative for evaluating exercise capacity in patients with a ventilatory limited exercise capacity, as well as to initiate an individually tailored exercise training program on the cycle ergometer.

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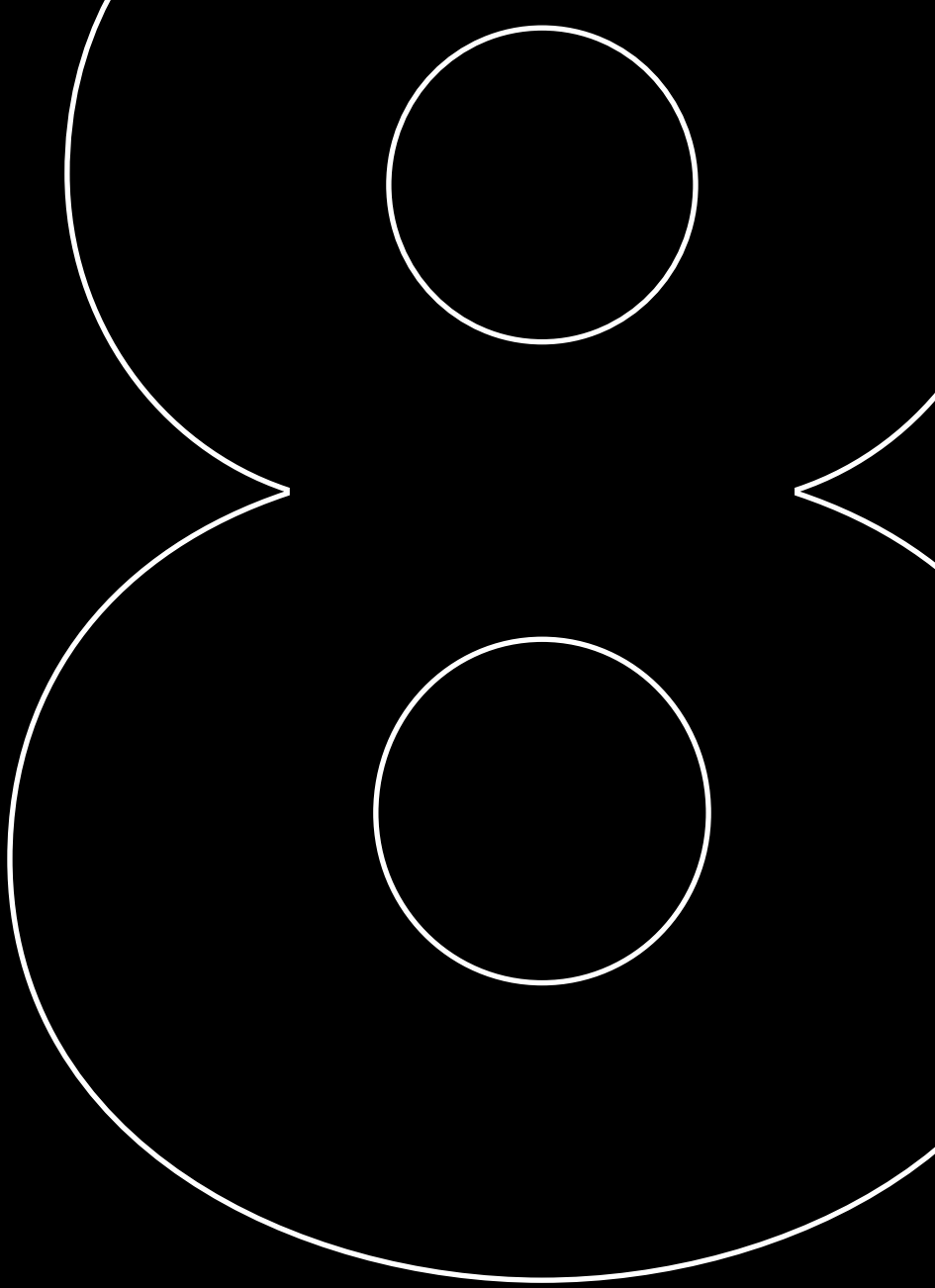

General discussion

Introduction

Cardiopulmonary exercise testing (CPET) is being increasingly utilized in daily (clinical) practice.[1-6] Whereas CPET initially was utilized to provoke cardiac arrhythmias, as well as to assess myocardial ischemia and exercise-induced bronchoconstriction, it nowadays also serves an important role in assessing aerobic exercise capacity, by measuring peak oxygen uptake ($V\dot{O}_{2peak}$), in children and adults with an extensive range of chronic conditions. Specific indications for pediatric CPET are listed in *CHAPTER 1*, TABLE 1. However, there are several factors that still limit the use of CPET in daily (clinical) practice. The constraints that coincide with performing CPET are described in detail in *CHAPTER 1*. These constraints have encouraged experts in the field of (clinical) exercise physiology to develop alternative measures, such as the oxygen uptake efficiency slope (OUES), as well as alternative exercise tests, such as the steep ramp test (SRT), to evaluate aerobic exercise capacity.

In the first part of this thesis, the usefulness of the OUES as an exercise intensity independent measure of aerobic exercise capacity was assessed. The characteristics of the OUES were investigated in healthy children and were described in *CHAPTER 2*. Subsequently, the validity of the OUES was assessed in two different pediatric patient populations. *CHAPTER 3* addressed the validity of the OUES in children with congenital heart disease (CHD), whereas in *CHAPTER 4*, the validity of the OUES in children with cystic fibrosis (CF) was evaluated.

The major findings of the first part of this thesis are:

- The OUES increases linearly with age in healthy boys and girls aged 8 to 17 years; due to the large inter-individual differences in OUES values, it is recommended to normalize OUES values for a measure of body size, preferably fat free mass (FFM) or body surface area (BSA) (*CHAPTER 2*);
- The OUES is a valid measure of aerobic exercise capacity in healthy children between the ages of 8 and 17 years, and in children with CHD (patients with a Fontan repair and patients with a surgical repair for tetralogy of Fallot, aged 8 to 19 years), which is independent of the achieved exercise intensity above the ventilatory threshold (VT) (*CHAPTER 2* and *CHAPTER 3*);
- Comparable to $V\dot{O}_{2peak}$, the OUES is able to differentiate between healthy children and children with CHD concerning aerobic exercise capacity, and, within CHD, between patients with a Fontan circulation and patients who had undergone surgical repair for tetralogy of Fallot (*CHAPTER 3*);

- The OUES appears to be of limited value in children with CF between the ages of 11 and 19 years, since it was dependent on the achieved exercise intensity, correlated only moderately with the more established measures of aerobic exercise capacity, and was not able to differentiate between healthy children and children with CF (*CHAPTER 4*).

The second part of this thesis covered studies that investigated the applicability of the SRT to provide an indication concerning a child's aerobic exercise capacity, while not requiring respiratory gas analysis measurements. The reliability and validity of the SRT were evaluated in a group of healthy children and were described in *CHAPTER 5*. Norm values for SRT performance were collected in healthy children and were presented in *CHAPTER 6*. Finally, the characteristics of the SRT in children with CF were evaluated and were described in *CHAPTER 7*.

The major findings of the second part of this thesis are:

- The SRT is a reliable and valid exercise test, which can predict $V\dot{O}_{2peak}$ in healthy children and adolescents aged 8 to 19 years (*CHAPTER 5*);
- In boys, aged between 8 and 19 years, the work rate at peak exercise (WR_{peak}) achieved at the SRT demonstrated an almost linear increase with age, even when normalized for body mass (*CHAPTER 6*);
- In girls, aged between 8 and 19 years, WR_{peak} attained at the SRT increased constantly until the age of approximately 13 years, where after values started to level off; normalized for body mass, WR_{peak} showed only a slight increase with age in girls, with a slight decrease as of the age of 14 years (*CHAPTER 6*);
- SRT performance was strongly correlated to $V\dot{O}_{2peak}$ achieved during regular CPET in healthy children aged 8 to 19 years, and in children with CF aged 11 to 19 years (*CHAPTER 5* and *CHAPTER 7*);
- As the SRT was well-tolerated and cardiopulmonary less demanding than regular CPET, it can be used as an alternative for evaluating exercise capacity in less motivated children, as well as in patients with a ventilatory limited exercise capacity (*CHAPTER 5* and *CHAPTER 7*).

Issues that have not been addressed or have not been discussed in detail in the previous chapters will be highlighted in the subsequent paragraphs.

The oxygen uptake efficiency slope

Physiology of the oxygen uptake efficiency slope

The main advantage of the OUES in comparison to $V\dot{O}_{2peak}$ is the fact that, theoretically, its linearity throughout the last part of CPET makes it resistant to disruption by early termination of the exercise test.[7-16] In other words, the OUES is supposed to not be largely influenced by the level of exertion achieved by the participant. Accompanied by a study in healthy children[15] and a study in obese children,[11] *CHAPTER 2* and *CHAPTER 3* confirm this theoretical construct of the OUES in healthy children and in children with CHD respectively. In contrast however, two other studies, in a combined group of healthy children and children with various heart diseases[7] and in a group of overweight children,[17] found that submaximal OUES values differed significantly from maximal OUES values. *CHAPTER 4* confirmed this nonlinearity of the OUES in children with CF. The nonlinearity of the OUES was explained by a post hoc analysis, which revealed that in children with CF, the course of the ventilatory efficiency throughout CPET was different compared to their healthy peers.

Physiologically, ventilatory efficiency (ventilatory equivalent for oxygen; $\dot{V}_E/\dot{V}O_2$) increases towards the VT during progressive CPET. This can be explained by an increase in the difference between mixed venous and arterial oxygen content, facilitating oxygen extraction from alveolar gas. Moreover, the increase in tidal volume results in decreased ventilatory dead space ventilation ($\dot{V}_D/\dot{V}_T$ ratio). Finally, matching of the ventilation to pulmonary perfusion is improved during the initial phase of CPET. In contrast, ventilatory efficiency decreases when exercise progresses above the VT, since $\dot{V}_E$ starts to increase excessively in relation to the increase in $\dot{V}O_2$.[18,19] This point indicates the shift to a greater contribution of anaerobic glycolysis as an additional source of energy when the cardiopulmonary system fails to deliver a sufficient amount of oxygen to the exercising muscles, in order to sustain oxidative metabolism during progressive exercise. Lactic acid is a by-product of anaerobic glycolysis, and will be almost completely dissociated in the serum where it is rapidly buffered.[20,21] The buffering of lactic acid raises the partial tension of carbon dioxide in the venous blood, thereby stimulating the ventilatory control mechanisms that augment $\dot{V}_E$ in order to eliminate carbon dioxide by the lungs and maintain blood homeostasis. As a consequence, a disproportional exponential increase in $\dot{V}_E$, compared to the increase in $\dot{V}O_2$, will be observed.[22]

Hence, it can be concluded that the highest OUES values occur around the VT, which has been confirmed recently.[23] This indicates that, around the VT, an increase in V_E is accompanied by the relatively largest increase in V_{O_2}.[23] The latter results in the lowest values observed for the V_E/V_{O_2}. This is in agreement with other studies, reporting that the lowest values of the V_E/V_{O_2} plotted against time, or the highest values of its inverse (V_{O_2}/V_E), the oxygen uptake efficiency (OUE) plotted against time, occur around the VT.[24,25] Consequently, Niemeijer *et al.*[23] recommended that OUES values of participants that did not achieve the VT should be interpreted with caution. In addition, the presence of a V_{O_2} plateau was found to reduce the value of the OUES.[16,23]

Interchangeability with peak oxygen uptake

Most available submaximal variables for aerobic exercise capacity were validated based on their correlation with $V_{O_{2peak}}$.[26] However, a strong correlation between two measures does not proof the interchangeability of these measures.[27,28] Therefore, previous studies predicted $V_{O_{2peak}}$ from OUES values, and used Bland-Altman plots to validate the OUES as a measure of aerobic exercise capacity.[10,17,29] Although these studies reported no significant differences between the measured $V_{O_{2peak}}$ and the $V_{O_{2peak}}$ predicted by the OUES, a significant bias was found. Hence, it seems that the OUES is not interchangeable with $V_{O_{2peak}}$. However, the OUES was not introduced by Baba *et al.*[7] with the purpose to predict $V_{O_{2peak}}$, nor to replace $V_{O_{2peak}}$ measurements. The OUES itself provides an objective and independent measure of aerobic exercise capacity, reflecting cardiopulmonary function as indicated by the efficiency of the V_E in relation to the oxygen uptake (V_{O_2}) during progressive exercise. Additionally, progressive CPET up to maximal exertion yields specific information regarding adaptations of the cardiopulmonary system during progressive exercise, which does not always occur during submaximal exercise testing.

Norm values for the oxygen uptake efficiency slope

Several studies,[15,31] as well as *CHAPTER 2* of the current thesis, stated that there is a need for appropriate pediatric norm values for the OUES. Recently, the normal physiological response to progressive CPET was assessed in a large group of healthy, non-athletic Dutch children and adolescents.[30] Norm values were constructed for a large number of measured exercise variables and their derivatives. The OUES was calculated using all acquired exercise data in 114 boys and 100 girls, ranging in age from 8 to 18 years. The results showed that OUES values increase with age in boys and girls,[30] which is in agreement with the results

described in *CHAPTER 2* of this thesis. More specifically, data in FIGURE 19 demonstrate that absolute 50th percentile values for the OUES increase linearly up to approximately 12 years of age in boys. Hereafter, a slightly steeper increase was observed. Eight-year-old boys reached absolute OUES values of 1,400, whereas 12-year-old boys achieved values of 2,100, and 18-year-old boys attained values of 3,500. Throughout the entire age range, values increased by 150% in boys. FIGURE 20 shows that absolute 50th percentile values for the OUES in girls increase linearly with age throughout the entire age range. Eight-year-old girls attained absolute OUES values of 1,200, and 18-year-old girls reached values of 2,600, representing an increase of 117% throughout childhood.

Studies in pediatric populations that have examined the relationship between the OUES and different anthropometric variables, reported that the OUES correlates highly with body mass, body height, body mass index (BMI), BSA, FFM, and age in healthy children[15] and in obese children.[11] These high correlation coefficients were confirmed by the study described in *CHAPTER 2*. Based on the results of the study described in *CHAPTER 2*, OUES values should be normalized for BSA or FFM in order to reduce the large inter-individual variation in OUES values in childhood. Though, in the study that established norm values for a large number of exercise variables obtained from CPET data, OUES values were only normalized for body size by dividing absolute OUES values by body mass.[30] FIGURE 21 and FIGURE 22 depict these relative OUES values in healthy boys and girls respectively. In both boys and girls, 50th percentile values for the OUES, normalized for body mass, remained more or less stable throughout the entire age range, roughly ranging between 48 and 49 and between 42 and 41 respectively.

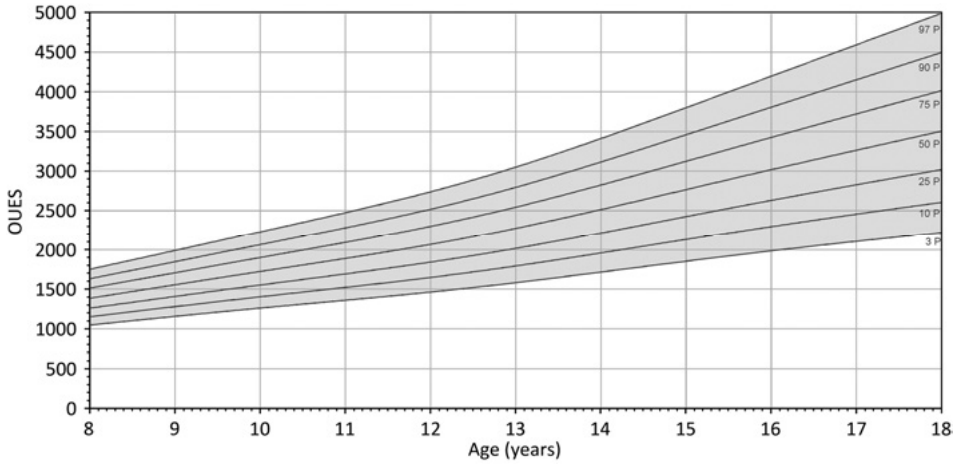

FIGURE 19. Absolute OUES values in boys.

ABBREVIATION: OUES=oxygen uptake efficiency slope.
NOTE: adapted from Bongers *et al.*[30]

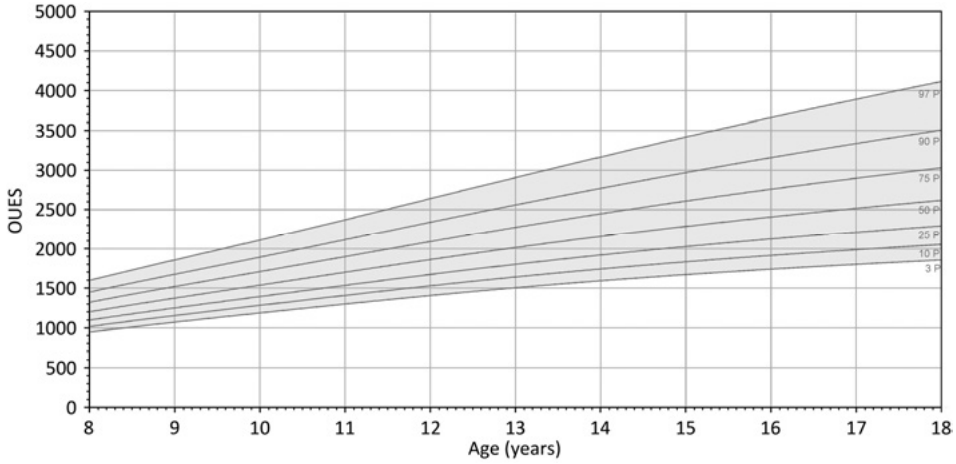

FIGURE 20. Absolute OUES values in girls.

ABBREVIATION: OUES=oxygen uptake efficiency slope.
NOTE: adapted from Bongers *et al.*[30]

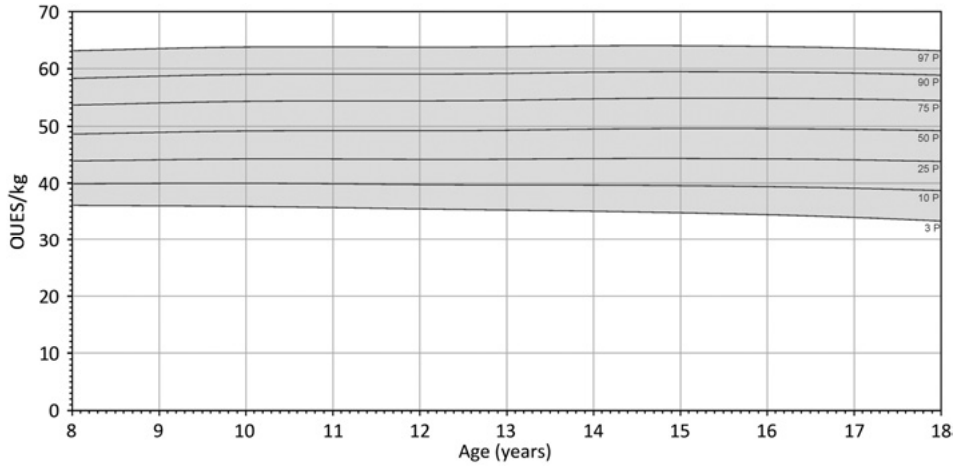

FIGURE 21. OUES values, normalized for body mass, in boys.

ABBREVIATION: OUES=oxygen uptake efficiency slope.
NOTE: adapted from Bongers *et al*.[30]

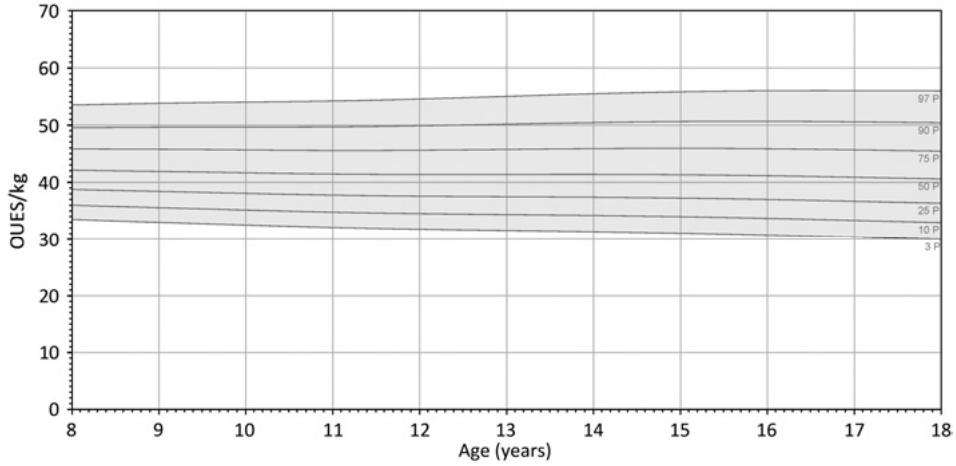

FIGURE 22. OUES values, normalized for body mass, in girls.

ABBREVIATION: OUES=oxygen uptake efficiency slope.
NOTE: adapted from Bongers *et al*.[30]

Conclusions and practical implications

- The OUES provides a valid measure of aerobic exercise capacity that is independent of the achieved exercise intensity above the VT in healthy children and in children with CHD, specifically in children with a Fontan repair and in children with surgical repair for tetralogy of Fallot;
- The OUES correlates highly with $V\dot{O}_{2peak}$ and the VT in these pediatric populations, reflecting cardiopulmonary function as indicated by the efficiency of ventilation;
- The OUES should not be utilized as a substitute for $V\dot{O}_{2peak}$ measurements;
- Interpretation of attained OUES values should be based on comparison with adequate norm values, comparisons between (groups of) participants, or evaluations within a participant;
- It is recommended to normalize absolute OUES values for body size in childhood and adolescence, preferably for FFM or BSA, since this will reduce the large inter-individual variation in OUES values;
- It is recommended to encourage the child to continue exercising as long as possible towards $V\dot{O}_{2peak}$ in order to gain as many data points for the calculation of the OUES, since associations with other exercise variables (e.g. $V\dot{O}_{2peak}$ and the VT) strengthened when more data points were used for its determination;
- It is recommended to calculate the OUES using all exercise data, except when a plateau in $V\dot{O}_2$ ($V\dot{O}_{2max}$) is achieved, since previous studies reported that the presence of a $V\dot{O}_2$ plateau reduces the value of the OUES[16,23];
- In children with CF, the OUES seems to be of limited value as an effort-independent measure of aerobic exercise capacity, due to its nonlinearity during the last part of CPET, as well as its limited distinguishing ability and its moderate correlations with $V\dot{O}_{2peak}$ and with the VT.

The steep ramp test

A screening tool for aerobic exercise capacity

The main advantage of the SRT compared to CPET is the fact that it does not require respiratory gas analysis measurements. Additionally, a strong correlation coefficient has been previously reported between the WR_{peak} attained at the SRT and the $V\dot{O}_{2peak}$ reached during CPET.[32] This strong relationship was confirmed in *CHAPTER 5* of the current thesis, and indicates that the SRT might be useful as a non-sophisticated screening tool that provides information concerning a child's aerobic exercise capacity. The prediction equation established in *CHAPTER 5* can be used by clinicians and researchers to predict aerobic exercise capacity in healthy children within a wide age-range (between 8 and 18 years of age). However, the conversion to $V\dot{O}_{2peak}$ might be of less interest, since sex- and age-related pediatric norm values for SRT performance (WR_{peak}) have been constructed in *CHAPTER 6*. For clinicians and researchers, these norm values facilitate adequate interpretation of SRT performance in healthy children and adolescents between 8 and 18 years of age.

Determining training intensity and monitoring training progress

In *CHAPTER 5* and *CHAPTER 7*, it was found that the WR_{peak} attained at the SRT correlated strongly with $V\dot{O}_{2peak}$ achieved during CPET in healthy children and patients with CF respectively. Perhaps most importantly, the SRT was found to be safe, well-tolerated, and cardiopulmonary less demanding than CPET. The SRT was originally introduced in order to determine and optimize interval exercise training intensity and to monitor training progress in adult patients with chronic heart failure.[33,34] In these studies, the SRT proved to be safe and practical in its use for prescribing interval exercise training intensity and monitoring training progress.[33-35] Since then, the SRT has been applied in various adult patient groups, including chronic obstructive pulmonary disease,[36] type 2 diabetes,[37] chronic heart failure,[38-41] and cancer,[32,42-44] for prescribing high-intensity exercise training (HIT), as well as for monitoring exercise training progress.

A case study of Hulzebos *et al*.[45] demonstrated that six weeks of HIT in a ventilatory limited adolescent patient with CF resulted in a 19% increase in $V\dot{O}_{2peak}$ and a 16% increase in WR_{peak} during CPET. Training intensity was based on SRT performance, which was measured every two weeks in order to adjust training WR according to the achieved improvements in SRT performance. Since children's physical activity patterns are characterized by short intense bursts of activity,[46]

HIT might be an appropriate method to improve exercise tolerance, because it involves significant anaerobic energy utilization. Therefore, it is believed to better mimic the physiological requirements of activities of daily living in children.[47] Due to its short duration, the SRT can be performed regularly, and, consequently, it is easy to incorporate this test in an exercise training program.[32] Nevertheless, HIT intensity may be best prescribed based on tests of anaerobic power and capacity, such as the Wingate Anaerobic Test (WAnT), which is considered to be the gold standard for anaerobic exercise capacity.[48] However, the WAnT has not been widely used[49] and requires a sophisticated cycle ergometer, including specific software.

Conclusions and practical implications

- The SRT is a feasible, reliable, and valid exercise test on a cycle ergometer in healthy children;
- SRT performance provides an indication of a child's aerobic exercise capacity, given that the main outcome measure of the SRT (WR_{peak}) was strongly correlated to the $\dot{V}O_{2peak}$ achieved during regular CPET in healthy children and children with CF;
- As the SRT was well-tolerated and cardiopulmonary less demanding than regular CPET, it can potentially be used as an alternative for evaluating exercise capacity in less motivated children, as well as in patients with a ventilatory limited exercise capacity;
- Based on the pediatric norm values described in *CHAPTER 6*, it is recommended to use the third percentile of the presented reference curves as a cut-off point to indicate below normal SRT performance;
- Since the SRT should not be used as a substitute for performing CPET, it is recommended to refer children with a significantly reduced SRT performance for extensive progressive CPET;
- The SRT can be used as a feasible alternative for evaluating exercise capacity, and can possibly be used to initiate an individually tailored exercise training program on the cycle ergometer.

Directions for future research

Results from studies in adults suggest that the OUES increases following an exercise training program in patients with coronary artery disease,[50] as well as in patients with heart failure.[51] The training-induced changes in the OUES were similar to those in $V\text{O}_{2\text{peak}}$,[50,51] indicating that the OUES is sensitive to improvements in aerobic exercise capacity. Since the responsiveness of the OUES to an exercise training program has never been addressed in pediatric populations, it would be interesting to investigate whether the OUES is clinically useful in pediatric populations to monitor changes in aerobic exercise capacity, particularly in children who can only perform submaximal exercise.

It would also be interesting to investigate the characteristics of the plateau in OUE (OUEP) in healthy children, as well as in pediatric patient populations in order to evaluate its clinical utility. The OUEP can be obtained by plotting the OUE ($V\text{O}_2/V\text{E}$) against time throughout CPET. OUE reaches its highest values, termed the OUEP, around the VT,[30] where after OUE values start to decline in response to hyperventilation, stimulated by lactic acid as a by-product of anaerobic glycolysis. Hence, the OUEP does not require maximal exercise. In two previous studies, the OUEP could be determined in each participant, in which it primarily reflected cardiovascular function, and appeared to be prognostically superior to the more established CPET variables, including $V\text{O}_{2\text{peak}}$, the VT, the $V\text{E}/V\text{CO}_2$-slope, and the oxygen pulse at peak exercise, in evaluating adult patients with chronic heart failure.[30,31]

In order to further evaluate the usefulness of the SRT in daily (clinical) practice, future studies should investigate the reliability and validity of the SRT in pediatric patient populations, as well as the discriminative properties of the SRT in different pediatric populations. In order to gain more knowledge concerning the physiological requirements of the SRT, it would be interesting to examine the exact contribution of the oxidative metabolism and anaerobic glycolysis during the SRT in healthy children and pediatric patient populations. Further research is also necessary to investigate the responsiveness of the SRT after an HIT program in healthy children and pediatric patient populations, in order to evaluate whether the SRT can be used to determine training intensity and monitor training progress. Finally, future studies should investigate whether HIT, monitored by SRT performance, is a better alternative than traditional aerobic exercise training programs.

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Summary

In *CHAPTER 1*, an extensive general introduction is given concerning pediatric exercise testing in order to assess aerobic exercise capacity. Measuring maximal oxygen uptake ($V\dot{O}_{2max}$) during progressive cardiopulmonary exercise testing (CPET) up to maximal exertion is widely recognized as the best single measure of aerobic exercise capacity. It is an important determinant of health, even in childhood and adolescence. Measuring $V\dot{O}_{2max}$ facilitates an accurate and objective assessment of the integrative physiological response to exercise of the pulmonary, cardiovascular, hematopoietic, and metabolic systems, and can be used for diagnostic, prognostic, and evaluative purposes.

Determining $V\dot{O}_{2max}$ requires a plateau in oxygen uptake ($V\dot{O}_2$), despite an increasing work rate (WR). Particularly in pediatric populations, a clear plateau in $V\dot{O}_2$ is seldom attained. Therefore, the $V\dot{O}_2$ at peak exercise ($V\dot{O}_{2peak}$) is often used as a substitute for $V\dot{O}_{2max}$. However, the attained $V\dot{O}_{2peak}$ is normally only considered valid when the child achieved a heart rate (HR) at $V\dot{O}_{2peak}$ of at least ≥95% of 195 beats·min^{-1} and a respiratory exchange ratio (RER) at $V\dot{O}_{2peak}$ of at least ≥1.00 as criteria for a maximal effort. Nevertheless, it still remains unclear whether the child has really performed a maximal effort when meeting these criteria. Additional limitations for $V\dot{O}_{2max}$ and $V\dot{O}_{2peak}$ are the fact that they are strongly influenced by the child's motivation, the selected exercise protocol, verbal encouragement, and the skills and experience of the tester to determine peak exercise. Lastly, performing CPET up to maximal exertion is not feasible in children or adolescents where maximal exercise testing is contraindicated, or when performance may be impaired by pain, shortness of breath, or fatigue rather than exertion.

Due to these limitations, experts developed alternative indices that do not rely on a maximal effort, such as the oxygen uptake efficiency slope (OUES). The OUES includes a submaximal parameter of aerobic exercise capacity that can be calculated by using exercise data collected during progressive CPET in addition to the measured $V\dot{O}_{2peak}$, or might even act as an alternative for $V\dot{O}_{2peak}$. It describes the relationship between the $V\dot{O}_2$ and the common logarithm of the minute ventilation ($V\dot{E}$) throughout CPET. The linearity of this relationship during the last part of CPET implies that the use of submaximal exercise data does not significantly alter the value of the OUES. This is an essential characteristic when a participant is either unwilling or unable to complete CPET up to maximal exertion. Although the OUES appears to be a promising measure of aerobic exercise capacity, more

profound investigation concerning its validity is necessary in healthy children, as well as in pediatric patient populations, before it can be implemented in daily pediatric (clinical) practice.

Performing respiratory gas analysis measurements throughout CPET, required for $V\dot{O}_{2peak}$ and OUES measurements, is sometimes not feasible in extramural care, due to the expense, the need for special equipment, and the required trained staff. Moreover, the use of a facemask or mouthpiece might frighten children. Due to these limitations, standardized CPET remains underused in daily (clinical) practice, which underlines the need for non-sophisticated pediatric exercise testing procedures that do not require respiratory gas analysis measurements. Such a test might help to increase the utilization of pediatric exercise testing.

The steep ramp test (SRT) is an incremental exercise test up to maximal exertion performed on a cycle ergometer that does not require respiratory gas analysis measurements. The attained peak WR (WR_{peak}) is the SRT's primary outcome measure that largely exceeds the WR_{peak} achieved during regular CPET. The latter is caused by the fast WR increments, which also results in a significantly reduced test duration compared to CPET. Since the attained WR_{peak} at the SRT correlates strongly with the $V\dot{O}_{2peak}$ attained during traditional CPET, the SRT might be useful as a simple screening tool that provides the clinician with an indication about a child's aerobic exercise capacity. However, prior to implementing the SRT in daily pediatric (clinical) practice, knowledge is required concerning its reliability and validity in healthy children, as well as in pediatric patient populations.

In the first part of this thesis, three studies are presented in which the validity of the OUES has been investigated in healthy children, in children with congenital heart disease (CHD), and in children with cystic fibrosis (CF).

Since the OUES has originally been introduced as a submaximal measure of cardiopulmonary function, the characteristics of the submaximal OUES in healthy children were investigated in *CHAPTER 2*. The results showed that the submaximal OUES was not significantly different than the maximal OUES (2201 ± 694 versus 2207 ± 704; P=0.296). Moreover, the submaximal OUES correlated highly with $V\dot{O}_{2peak}$ (r=0.88; P<0.01), peak $V\dot{E}$ ($V\dot{E}_{peak}$: r=0.73; P<0.01), the ventilatory threshold (VT: r=0.85; P<0.01), and different anthropometric variables (r values ranging from 0.53 to 0.84; with P<0.01 for all coefficients). Therefore, it was concluded that the submaximal OUES could provide an objective, independent measure of cardiopulmonary function in children, reflecting efficiency of ventilation. It is suggested

to express OUES values relative to body surface area (BSA; OUES/BSA) or fat free mass (FFM) in order to reduce the large inter-individual differences.

In *CHAPTER 3*, the validity of the OUES in children with CHD was evaluated. Children with a Fontan circulation and children who had undergone surgical repair for tetralogy of Fallot (ToF) were included in this study. Results demonstrated that in all three groups, the OUES/BSA values determined at the three different exercise intensities were not significantly different from each other. OUES/BSA values were significantly reduced in the children with CHD (1237 ± 279 versus 1576 ± 186; $P<0.001$), with significantly lower values in the Fontan patients compared to ToF patients (1108 ± 234 versus 1374 ± 262; $P<0.001$). Moderate to strong correlations were found between the OUES/BSA and both the $V\text{O}_{2\text{peak}}$ (r values ranging from 0.324, not significant, to 0.750; with $P<0.05$ for the other coefficients) and the VT (r values ranging from 0.536 to 0.775; with $P<0.05$ for all coefficients) in both Fontan and ToF patients. In conclusion, it was reported that the OUES provides a valid measure of aerobic exercise capacity in children with CHD, which is independent of exercise intensity and correlates strongly with $V\text{O}_{2\text{peak}}$ and the VT. Similar to $V\text{O}_{2\text{peak}}$, the OUES was found to be capable of differentiating between healthy children and children with CHD, as well as between Fontan and ToF patients.

The validity of the OUES in children with CF was examined in the study presented in *CHAPTER 4*. Results showed that, despite the fact that $V\text{O}_{2\text{peak}}$ was significantly reduced in patients with CF (40.9 ± 7.8 versus 49.9 ± 7.9 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; $P<0.001$), only the OUES/BSA that was calculated using the first 50% of the exercise data was significantly different between the groups (1378 ± 295 versus 1616 ± 333; $P=0.016$). OUES/BSA values determined at different exercise intensities differed significantly within patients with CF (1378 ± 295, 1542 ± 328, and 1610 ± 336 using the first 50% of the exercise data, using the first 75% of the exercise data, and using 100% of the exercise data respectively). By performing a post hoc analysis, it was demonstrated that the latter results can be explained by the fact that the efficiency of ventilation in children with moderate CF was significantly reduced during submaximal exercise when compared to their healthy peers. During the last part of CPET, the children with CF approached the values for the efficiency of ventilation attained by their healthy peers. Nevertheless, the OUES/BSA correlated only moderately with $V\text{O}_{2\text{peak}}$ (r values ranging from 0.411 to 0.536; with $P<0.05$ for all coefficients) and the VT (r values ranging from 0.350, not significant, to 0.541; with $P<0.05$ for the other coefficients). Therefore, it was reported that the OUES is not a valid submaximal measure of aerobic exercise capacity in children with mild to moderate CF, due to its limited distinguishing properties, its nonlinearity throughout progressive exercise, and its moderate correlation with $V\text{O}_{2\text{peak}}$ and the VT.

The second part of this thesis presents three studies that addressed the applicability of the SRT as a non-sophisticated pediatric exercise test that provides information about a child's aerobic exercise capacity, without the use of respiratory gas analysis measurements.

In *CHAPTER 5*, the reliability and validity of the SRT was evaluated in healthy children and adolescents. Reliability statistics for the WR_{peak} values attained at the two SRTs showed an intraclass correlation coefficient of 0.986 (P<0.001). The average difference between the two SRTs was -6.4 W, with limits of agreement between +24.5 and -37.5 W. A high correlation between the WR_{peak} attained at the SRT and the $V\dot{O}_{2peak}$ achieved during CPET was found (r=0.958; P<0.001). Stepwise linear regression analysis provided the following prediction equation that can be used to estimate the $V\dot{O}_{2peak}$ attained during CPET with the achieved WR_{peak} at the SRT: $V\dot{O}_{2peak}$ (mL·min^{-1}) = (8.262 × WR_{peak} SRT) + 177.096 (R^2=0.917, standard error of the estimate=237.4). The significantly lower values for the attained peak HR (HR_{peak}: 181 ± 10 versus 193 ± 9 beats·min^{-1}; P<0.001) and the achieved peak $V\dot{E}$ ($V\dot{E}_{peak}$: 80.7 ± 30.2 versus 93.3 ± 30.7 L·min^{-1}; P<0.001) at the SRT compared to CPET in the validity group indicate that the SRT is cardiopulmonary less demanding than regular CPET. In conclusion, it was reported that the SRT is a reliable and valid exercise test in healthy children and adolescents, which can be used to predict $V\dot{O}_{2peak}$ and is cardiopulmonary less demanding than CPET.

The objective of the study described in *CHAPTER 6* was to provide sex- and age-related norm values for SRT performance in healthy children and adolescents between the ages of 8 and 19 years. WR_{peak} correlated highly with age, body mass, body height, BSA, and FFM in boys and girls (r values ranging from 0.811 to 0.930; with P<0.001 for all coefficients). The reference curves demonstrated an almost linear increase with age in WR_{peak} in boys, even when normalized for body mass. In contrast, absolute WR_{peak} in girls increased constantly until the age of approximately 13 years, where after WR_{peak} started to level off. WR_{peak} normalized for body mass showed only a slight increase with age in girls, with a slight decrease in relative WR_{peak} as of the age of 14 years. This study facilitates the interpretation of SRT results for clinicians and researchers by providing sex- and age-related norm values for SRT performance using reference centiles for both absolute and relative WR_{peak}.

The study presented in *CHAPTER* 7 aimed to evaluate SRT performance in children and adolescents with CF, as well as to compare the physiological responses to the SRT and regular CPET with each other. The results demonstrated that children and adolescents with CF attained values for absolute and relative WR_{peak} during the

SRT that corresponded respectively to 82 ± 14% and 92 ± 14% of predicted. Nutritional status and degree of airway obstruction did not influence SRT performance. Significantly higher values were attained for WR_{peak} at the SRT compared to CPET (252 ± 69 versus 174 ± 46 W; P<0.001), while significantly lower values were achieved for HR_{peak} (168 ± 14 versus 182 ± 12 beats·min^{-1}; P<0.001), $\dot{V}E_{peak}$ (59.2 ± 19.5 versus 72.0 ± 20.2 L·min^{-1}; P=0.006), and $\dot{V}O_{2peak}$ (36.9 ± 7.5 versus 41.5 ± 7.6 mL·kg^{-1}·min^{-1}; P=0.008). A strong correlation between WR_{peak} attained at the SRT and the $\dot{V}O_{2peak}$ achieved during CPET was found (r=0.822; P<0.001). Since the SRT was well-tolerated in patients with CF and seems to be cardiopulmonary less demanding than regular CPET, it could potentially be used as a feasible alternative for evaluating exercise capacity in patients with a ventilatory limited exercise capacity, as well as to initiate an individually tailored exercise training program on the cycle ergometer.

The general discussion in *CHAPTER 8* presents the main findings of this thesis, addresses issues that not have been discussed or not have been discussed in detail in the previous chapters, provides practical implications for clinicians and researchers, and presents directions for future research.

Samenvatting

In *HOOFDSTUK 1* is een uitgebreide algemene introductie gegeven betreffende het uitvoeren van inspanningstesten bij kinderen met als doel het meten van de aërobe inspanningscapaciteit. Het meten van de maximale zuurstofopname ($V\text{O}_{2max}$) tijdens een progressieve cardiopulmonale inspanningstest tot het punt van uitputting van de testpersoon is wereldwijd erkend als de gouden standaard voor aërobe inspanningscapaciteit. De aërobe inspanningscapaciteit, of $V\text{O}_{2max}$, is een belangrijke gezondheidsdeterminant, zelfs gedurende de kindertijd en adolescentie. Het bepalen van de $V\text{O}_{2max}$ is een betrouwbare en objectieve manier om de geïntegreerde fysiologische respons van het pulmonale, cardiovasculaire, hematopoëtische en metabole systeem ten aanzien van inspanning te evalueren, en kan worden gebruikt voor diagnostische, prognostische en evaluatieve doeleinden.

De bepaling van de $V\text{O}_{2max}$ vereist een plateau in de zuurstofopname ($V\text{O}_2$), ondanks een toenemende belasting. Voornamelijk in pediatrische populaties wordt een duidelijk plateau in $V\text{O}_2$ slechts zelden behaald. Daarom wordt de $V\text{O}_2$ die gemeten wordt op piek (of maximale) inspanning ($V\text{O}_{2peak}$) vaak gebruikt als alternatief voor $V\text{O}_{2max}$. Echter, de behaalde $V\text{O}_{2peak}$ wordt over het algemeen alleen als valide beschouwd wanneer de hartslagfrequentie van het kind op $V\text{O}_{2peak}$ ten minste ≥95% van 195 slagen·min^{-1} bedroeg en de respiratoire gaswisselingsverhouding op $V\text{O}_{2peak}$ ten minste ≥1,00 was. Het blijft echter alsnog de vraag of het kind een ware maximale inspanning geleverd heeft, wanneer aan deze criteria voor een maximale inspanning voldaan zijn. Een additionele beperking van de $V\text{O}_{2max}$ en $V\text{O}_{2peak}$ is het feit dat beiden sterk afhankelijk zijn van de motivatie van het kind, het geselecteerde inspanningsprotocol, verbale aanmoedigingen en ook van de vaardigheden en ervaring van de testleider voor het bepalen van piek (maximale) inspanning. Tot slot is het uitvoeren van een reguliere cardiopulmonale inspanningstest tot het punt van uitputting niet haalbaar bij kinderen en adolescenten waarbij maximale inspanning gecontra-indiceerd is of waarbij inspanning gelimiteerd wordt door pijn, kortademigheid of vermoeidheid in plaats van door uitputting.

Vanwege deze beperkingen hebben experts alternatieve maten ontwikkeld die niet afhankelijk zijn van een maximale inspanning, waaronder de 'oxygen uptake efficiency slope' (OUES). De OUES is een submaximale maat voor aërobe inspanningscapaciteit die naast de $V\text{O}_{2peak}$ berekend kan worden met data verkregen middels ademgasanalyse, of zelfs als een alternatief voor de $V\text{O}_{2peak}$ kan fungeren. De OUES is de regressiecoëfficiënt van de lineaire relatie tussen de $V\text{O}_2$ en de (Briggse)

logaritme van het ademminuutvolume tijdens een cardiopulmonale inspanningstest (ventilatoire efficiëntie). De lineariteit van deze relatie gedurende het laatste deel van de test impliceert dat het gebruik van submaximale data verkregen via ademgasanalyse de waarde van de OUES (regressiecoëfficiënt) weinig doet veranderen. Dit is een essentiële eigenschap wanneer de testpersoon geen maximale inspanning wíl of kán uitvoeren. Hoewel de OUES een veelbelovende maat voor aërobe inspanningscapaciteit lijkt te zijn, is verder onderzoek naar de validiteit bij gezonde kinderen en pediatrische patiëntenpopulaties nodig alvorens de OUES geïmplementeerd kan worden in de dagelijkse (klinische) praktijk.

Ademgasanalyse tijdens een reguliere cardiopulmonale inspanningstest is soms niet mogelijk in de extramurale zorg (bijvoorbeeld in de huisartspraktijk of fysiotherapiepraktijk) vanwege de kosten, de benodigde ademgasanalyse-apparatuur en de noodzakelijke aanwezigheid van getraind personeel, terwijl ademgasanalyse juist vereist is voor het bepalen van zowel de $V\dot{O}_{2peak}$ en de OUES. Bovendien kan het gebruik van een gezichtsmasker of mondstuk een kind beangstigen. Door deze beperkingen blijft het uitvoeren van progressieve cardiopulmonale inspanningstesten onderbenut in de dagelijkse (klinische) praktijk, wat de behoefte aan ongecompliceerde procedures voor het uitvoeren van inspanningstesten bij kinderen onderstreept. Een eenvoudige test kan helpen om het gebruik van inspanningstesten bij kinderen te doen laten toenemen.

De zogenaamde 'steep ramp test' (SRT) is een progressieve inspanningstest op een fietsergometer waarbij de belasting snel toeneemt tot het punt van uitputting van de testpersoon. De SRT is een noncardiopulmonale inspanningstest en vereist dus geen ademgasanalyse. De maximaal behaalde belasting (WR_{peak}) is de SRT's primaire uitkomstmaat. Door de snelle toename van de belasting is de WR_{peak} op de SRT beduidend hoger en de testduur aanzienlijk korter vergeleken met de WR_{peak} en de testduur op de reguliere cardiopulmonale inspanningstest. Aangezien de WR_{peak} behaald op de SRT sterk correleert met de $V\dot{O}_{2peak}$ behaald op de cardiopulmonale inspanningstest, is de SRT wellicht bruikbaar als een eenvoudig screeningsinstrument dat de clinicus informatie verschaft over de aërobe inspanningscapaciteit van een kind. Echter, voordat de SRT geïmplementeerd kan worden in de dagelijkse pediatrische (klinische) praktijk is informatie betreffende de betrouwbaarheid en validiteit van de SRT bij gezonde kinderen en bij pediatrische patiëntenpopulaties essentieel.

In het eerste deel van dit proefschrift worden drie studies gepresenteerd waarin de validiteit van de OUES onderzocht is bij gezonde kinderen, bij kinderen met een congenitale hartaandoening en bij kinderen met taaislijmziekte (cystische fibrose

[CF]). Juist bij patiënten met een cardiopulmonale aandoening kan het voorkomen dat zij niet hun 'ware' $V_{O_{2peak}}$ behalen tijdens de reguliere cardiopulmonale inspanningstest, omdat slechts een submaximale inspanning geleverd is vanwege bijvoorbeeld kortademigheid of vermoeidheid.

Vanwege het feit dat de OUES oorspronkelijk geïntroduceerd is als een submaximale maat voor cardiopulmonale functie, zijn de eigenschappen van de submaximale OUES onderzocht in een gezonde pediatrische populatie in de studie beschreven in *HOOFDSTUK 2*. Cardiopulmonale inspanningstesten volgens het Godfrey protocol werden uitgevoerd bij 46 gezonde kinderen tussen de 7 en 17 jaar oud (27 jongens, gemiddelde ± standaarddeviatie [SD] leeftijd: 11,8 ± 2,2 jaar en 19 meisjes, gemiddelde ± SD leeftijd: 12,9 ± 2,6 jaar). De maximale OUES, de submaximale OUES, de $V_{O_{2peak}}$, het ademminuutvolume op piek (maximale) inspanning en de ventilatoire drempel werden vervolgens bepaald. De resultaten lieten zien dat de submaximale OUES niet significant verschilde van de maximale OUES (2201 ± 694 versus 2207 ± 704; P=0,296). Verder correleerde de submaximale OUES sterk met de $V_{O_{2peak}}$ (r=0,88; P<0,01), het ademminuutvolume op piek (maximale) inspanning (r=0,73; P<0,01), de ventilatoire drempel (r=0,85; P<0,01) en verschillende antropometrische variabelen (r waarden variërend van 0,53 tot 0,84; P<0,01 voor alle coëfficiënten). Op basis van de studieresultaten werd vervolgens geconcludeerd dat de submaximale OUES een objectieve maat is voor cardiopulmonale functie bij gezonde kinderen, welke onafhankelijk is van de geleverde inspanning en de efficiëntie van de ventilatie uitdrukt. Bovendien wordt aanbevolen om OUES-waarden te normaliseren voor lichaamsoppervlakte (OUES/BSA) of vetvrije massa, om zo de grote inter-individuele verschillen in OUES-waarden te reduceren.

In *HOOFDSTUK 3* is de validiteit van de OUES geëvalueerd bij kinderen met een congenitale hartaandoening. Eenendertig patiënten met een congenitale hartaandoening, waarvan 16 patiënten (gemiddelde ± SD leeftijd: 11,2 ± 2,7 jaar) met een Fontan circulatie en 15 patiënten (gemiddelde ± SD leeftijd: 13,2 ± 3,6 jaar) die een operatieve correctie voor tetralogie van Fallot hebben ondergaan, hebben een cardiopulmonale inspanningstest volgens het Godfrey protocol uitgevoerd. De OUES werd berekend en genormaliseerd voor lichaamsoppervlakte op drie verschillende inspanningsintensiteiten: (1) door 100% van de inspanningsdata te gebruiken; (2) door de eerste 75% van de inspanningsdata te gebruiken; en (3) door inspanningsdata tot aan de ventilatoire drempel te gebruiken. Verder zijn de $V_{O_{2peak}}$, de ventilatoire drempel, de regressiecoëfficiënt van de relatie tussen het ademminuutvolume en de zuurstofopname (V_E/V_{O_2}-slope) en de regressiecoëfficiënt van de relatie tussen het ademminuutvolume en de koolstofdioxideproductie (V_E/V_{CO_2}-slope) berekend en vergeleken met de behaalde waarden van de 46

gezonde kinderen (gemiddelde ± SD leeftijd: 12,2 ± 2,4 jaar) die getest zijn in de studie beschreven in *HOOFDSTUK 2*. De resultaten demonstreerden dat in alle drie de groepen de OUES/BSA-waarden berekend op de drie verschillende inspanningsintensiteiten niet significant van elkaar verschilden. OUES/BSA-waarden waren significant verlaagd bij kinderen met een congenitale hartaandoening (1237 ± 279 versus 1576 ± 186; P<0,001), met significant lagere waarden bij de patiënten met een Fontan circulatie vergeleken met de patiënten met een operatieve correctie voor tetralogie van Fallot (1108 ± 234 versus 1374 ± 262; P<0,001). Matig tot sterke correlaties werden gevonden tussen de OUES/BSA en de $V\text{O}_{2\text{peak}}$ (r waarden variërend van 0,324, niet significant, tot 0,606 en r waarden variërend van 0,571 tot 0,750; met P<0,05 voor de overige coëfficiënten) en tussen de OUES/BSA en de ventilatoire drempel (r waarden variërend van 0,536 tot 0,652 en r waarden variërend van 0,557 tot 0,775; met P<0,05 voor alle coëfficiënten), in patiënten met een Fontan circulatie en in patiënten met tetralogie van Fallot respectievelijk. Concluderend werd vervolgens gesteld dat de OUES een valide maat is voor aërobe inspanningscapaciteit bij kinderen met een congenitale hartaandoening, die onafhankelijk is van de behaalde inspanningsintensiteit en matig tot sterk correleert met de $V\text{O}_{2\text{peak}}$ en de ventilatoire drempel. Verder bleek de OUES, net als de $V\text{O}_{2\text{peak}}$, onderscheid te kunnen maken tussen gezonde kinderen en kinderen met een congenitale hartaandoening, alsook tussen patiënten met een Fontan circulatie en patiënten met een operatieve correctie voor tetralogie van Fallot.

De validiteit van de OUES bij patiënten met CF is onderzocht in de studie beschreven in *HOOFDSTUK 4*. Inspanningsdata van 22 kinderen met CF en milde tot matige luchtwegobstructie (13 jongens en 9 meisjes, gemiddelde ± SD leeftijd: 15,7 ± 1,5 jaar, gemiddelde ± SD geforceerd expiratoir secondevolume [FEV_1]: 82 ± 16% van voorspeld) die een cardiopulmonale inspanningstest volgens het Godfrey protocol hebben ondergaan werden geanalyseerd en vergeleken met de inspanningsdata van 22 gezonde kinderen (13 jongens en 9 meisjes, gemiddelde ± SD leeftijd: 14,2 ± 1,5 jaar). De OUES werd berekend op drie verschillende relatieve inspanningsintensiteiten: (1) door de eerste 50% van de inspanningsdata te gebruiken; (2) door de eerste 75% van de inspanningsdata te gebruiken; en (3) door 100% van de inspanningsdata te gebruiken. OUES-waarden werden vervolgens gecorrigeerd voor lichaamsoppervlakte. De resultaten lieten zien dat, ondanks het feit dat patiënten met CF significant lagere waarden voor $V\text{O}_{2\text{peak}}$ behaalden (40,9 ± 7,8 versus 49,9 ± 7,9 $mL \cdot kg^{-1} \cdot min^{-1}$; P<0,001), alleen de OUES/BSA berekend met de eerste 50% van de inspanningsdata significant verschillend was tussen de twee groepen (1378 ± 295 versus 1616 ± 333; P=0,016), met lagere waarden behaald door patiënten met CF. Bij kinderen met CF waren de OUES/BSA-waarden, berekend op de verschillende relatieve inspanningsintensiteiten, significant

verschillend van elkaar (1378 ± 295, 1542 ± 328 en 1610 ± 336 voor de OUES berekend met de eerste 50%, de eerste 75% en 100% van de inspanningsdata respectievelijk). Middels een post hoc analyse werd vervolgens aangetoond dat deze nonlineariteit van de OUES verklaard kan worden door het feit dat kinderen met milde tot matige CF minder efficiënt ademen gedurende submaximale inspanning vergeleken met gezonde leeftijdsgenoten. Gedurende het laatste deel van de maximale cardiopulmonale inspanningstest benaderden de patiënten met CF de waarden voor ademhalingsefficiëntie behaald door hun gezonde leeftijdsgenoten. Desalniettemin correleerde de OUES/BSA slechts matig met de $V\text{O}_{2peak}$ (r waarden variërend van 0,411 tot 0,536; met $P<0,05$ voor alle coëfficiënten) en de ventilatoire drempel (r waarden variërend van 0,350, niet significant, tot 0,541, met $P<0,05$ voor de overige coëfficiënten). Door deze bevindingen werd vervolgens geconcludeerd dat de OUES geen valide submaximale maat is voor aërobe inspanningscapaciteit bij kinderen met CF en milde tot matige luchtwegobstructie, vanwege een beperkt discriminerend vermogen, de nonlineariteit gedurende het laatste deel van de maximale cardiopulmonale inspanningstest en de matige correlaties met $V\text{O}_{2peak}$ en de ventilatoire drempel.

In het tweede deel van dit proefschrift zijn drie studies beschreven waarin de toepasbaarheid van de SRT is onderzocht bij gezonde kinderen en kinderen met CF. Er is nagegaan of de SRT gebruikt kan worden als een eenvoudige inspanningstest zonder ademgasanalyse, die een indicatie geeft van de aërobe inspanningscapaciteit van een kind. Tevens is de fysiologische respons ten aanzien van het uitvoeren van een SRT vergeleken met de fysiologische respons ten aanzien van het uitvoeren van een progressieve cardiopulmonale inspanningstest volgens het Godfrey protocol.

In *HOOFDSTUK 5* zijn de betrouwbaarheid en de validiteit van de SRT onderzocht bij gezonde kinderen en adolescenten. Vijfenzeventig kinderen werden gerandomiseerd ingedeeld in een betrouwbaarheidsgroep (n=37, 17 jongens en 20 meisjes, gemiddelde ± SD leeftijd: 13,9 ± 3,2 jaar) en een validiteitsgroep (n=38, 17 jongens en 20 meisjes, gemiddelde ± SD leeftijd: 13,9 ± 3,2 jaar). De deelnemers in de betrouwbaarheidsgroep hebben binnen twee weken tweemaal een SRT uitgevoerd, terwijl de deelnemers uit de validiteitsgroep binnen twee weken een SRT en een reguliere cardiopulmonale inspanningstest volgens het Godfrey protocol hebben uitgevoerd, beiden met ademgasanalyse. WR_{peak} was de primaire uitkomstmaat van de SRT en de $V\text{O}_{2peak}$ was de belangrijkste uitkomstmaat van de cardiopulmonale inspanningstest. Een 'intraclass' correlatiecoëfficiënt van 0,986 ($P<0,001$) werd gevonden voor de WR_{peak} behaald op de twee SRTs. Het gemiddelde verschil tussen de twee SRTs bedroeg -6,4 W, met 'limits of agreement' tussen +24,5 en

-37,5 W. Een hoge correlatiecoëfficiënt werd gevonden tussen de WR_{peak} behaald op de SRT en de $V\dot{O}_{2peak}$ behaald op de cardiopulmonale inspanningstest (r=0,958; *P*<0,001). Stapsgewijze lineaire regressieanalyse leverde de volgende predictievergelijking op: $V\dot{O}_{2peak}$ ($mL \cdot min^{-1}$) = (8,262 × WR_{peak} SRT) + 177,096 (R^2=0,917, standaardfout van de schatting=237,4). In de validiteitsgroep bleek de behaalde hartslagfrequentie op piek (maximale) inspanning (181 ± 10 versus 193 ± 9 slagen·min^{-1}; *P*<0,001), alsook het behaalde ademminuutvolume op piek inspanning (80,7 ± 30,2 versus 93,3 ± 30,7 $L \cdot min^{-1}$; *P*<0,001), significant lager te zijn tijdens de SRT vergeleken met de reguliere cardiopulmonale inspanningstest. Aan de hand van deze resultaten werd geconcludeerd dat de SRT een betrouwbare en valide inspanningstest is bij gezonde kinderen en adolescenten, die gebruikt kan worden om de $V\dot{O}_{2peak}$ te schatten en die cardiopulmonaal minder belastend is dan de cardiopulmonale inspanningstest.

Het doel van de studie beschreven in *HOOFDSTUK 6* was het opstellen van geslachts- en leeftijdsgerelateerde normwaarden voor kinderen en adolescenten tussen de 8 en 19 jaar voor de geleverde prestatie op de SRT. Tweehonderd en tweeënvijftig kinderen en adolescenten, 118 jongens (gemiddelde ± SD leeftijd: 13,4 ± 3,0 jaar) en 134 meisjes (gemiddelde ± SD leeftijd: 13,4 ± 2,9 jaar), hebben een SRT uitgevoerd waarbij de behaalde WR_{peak} de primaire uitkomstmaat was. Data werden gebruikt om normwaarden op te stellen in de vorm van centielen. De behaalde WR_{peak} correleerde sterk met leeftijd, lichaamsgewicht, lichaamslengte, lichaamsoppervlakte en vetvrije massa bij jongens en meisjes (r waarden variërend van 0,811 tot 0,930; met *P*<0,001 voor alle coëfficiënten). De normwaarden voor jongens lieten een bijna lineaire toename met leeftijd zien voor de behaalde WR_{peak}, zelfs wanneer de waarden genormaliseerd werden voor lichaamsgewicht. In tegenstelling tot de jongens lieten de normwaarden voor de behaalde WR_{peak} voor meisjes een lineaire toename met leeftijd zien tot ongeveer 13 jaar, waarna de waarden afvlakten. Gecorrigeerd voor lichaamsgewicht liet de behaalde WR_{peak} bij meisjes een lichte toename met leeftijd zien, met een lichte afname vanaf ongeveer 14 jaar. Deze studie faciliteert de interpretatie van het behaalde resultaat op de SRT voor clinici en onderzoekers met behulp van geslachts- en leeftijdsgerelateerde normwaarden, gepresenteerd als centielen, voor de behaalde absolute en relatieve WR_{peak}.

Het doel van de studie beschreven in *HOOFDSTUK 7* was het evalueren van de geleverde prestatie van kinderen en adolescenten met CF op de SRT, alsook het vergelijken van de fysiologische respons ten aanzien van de SRT met de fysiologische respons ten aanzien van de reguliere cardiopulmonale inspanningstest. Veertig kinderen en adolescenten met CF (17 jongens en 23 meisjes, gemiddelde ± SD

leeftijd: 14,7 ± 1,7 jaar, gemiddelde ± SD FEV_1: 86 ± 18% van voorspeld) voerden gerandomiseerd een SRT en een cardiopulmonale inspanningstest volgens het Godfrey protocol uit, beiden met ademgasanalyse. De behaalde WR_{peak}, de hartslagfrequentie op piek (maximale) inspanning, het ademminuutvolume op piek inspanning en de $\dot{V}O_{2peak}$ waren de belangrijkste uitkomstmaten. Kinderen en adolescenten met CF behaalden waarden op de SRT die overeenkwamen met 82 ± 14% en 92 ± 14% van voorspeld voor de absolute WR_{peak} en de WR_{peak} genormaliseerd voor lichaamsgewicht respectievelijk. Voedingsstatus en de mate van luchtwegobstructie hadden beiden geen invloed op de SRT prestatie. Vergeleken met de cardiopulmonale inspanningstest werden significant hogere waarden behaald voor de WR_{peak} op de SRT (252 ± 69 versus 174 ± 46 W; P<0,001), terwijl significant lagere waarden werden behaald op de SRT voor de hartslagfrequentie op piek inspanning (168 ± 14 versus 182 ± 12 slagen·min^{-1}; P<0,001), het maximaal ademminuutvolume op piek inspanning (59,2 ± 19,5 versus 72,0 ± 20,2 L·min^{-1}; P=0,006) en de $\dot{V}O_{2peak}$ (36,9 ± 7,5 versus 41,5 ± 7,6 mL·kg^{-1}·min^{-1}; P=0,008). Een sterke correlatie werd gevonden tussen de WR_{peak} behaald op de SRT en de $\dot{V}O_{2peak}$ behaald op de cardiopulmonale inspanningstest (r=0,822; P<0,001). Geconcludeerd werd dat de SRT wellicht gebruikt kan worden als een haalbaar alternatief voor de reguliere cardiopulmonale inspanningstest voor het evalueren van de inspanningscapaciteit bij patiënten met een ventilatoir gelimiteerde inspanningscapaciteit, omdat de SRT goed getolereerd werd door kinderen en adolescenten met CF en cardiopulmonaal minder belastend lijkt te zijn dan de cardiopulmonale inspanningstest. De SRT kan tevens gebruikt worden voor het opstellen van een individueel trainingsprogramma op een fietsergometer.

In de algemene discussie beschreven in *HOOFDSTUK 8* worden de hoofdbevindingen van dit proefschrift gepresenteerd, worden punten bediscussieerd die nog niet, of niet in detail, besproken zijn in de eerdere hoofdstukken, worden de praktische implicaties voor clinici en onderzoekers voortkomend uit dit proefschrift besproken en worden suggesties voor toekomstig onderzoek gedaan.

Conclusies en praktische implicaties

'Oxygen uptake efficiency slope'

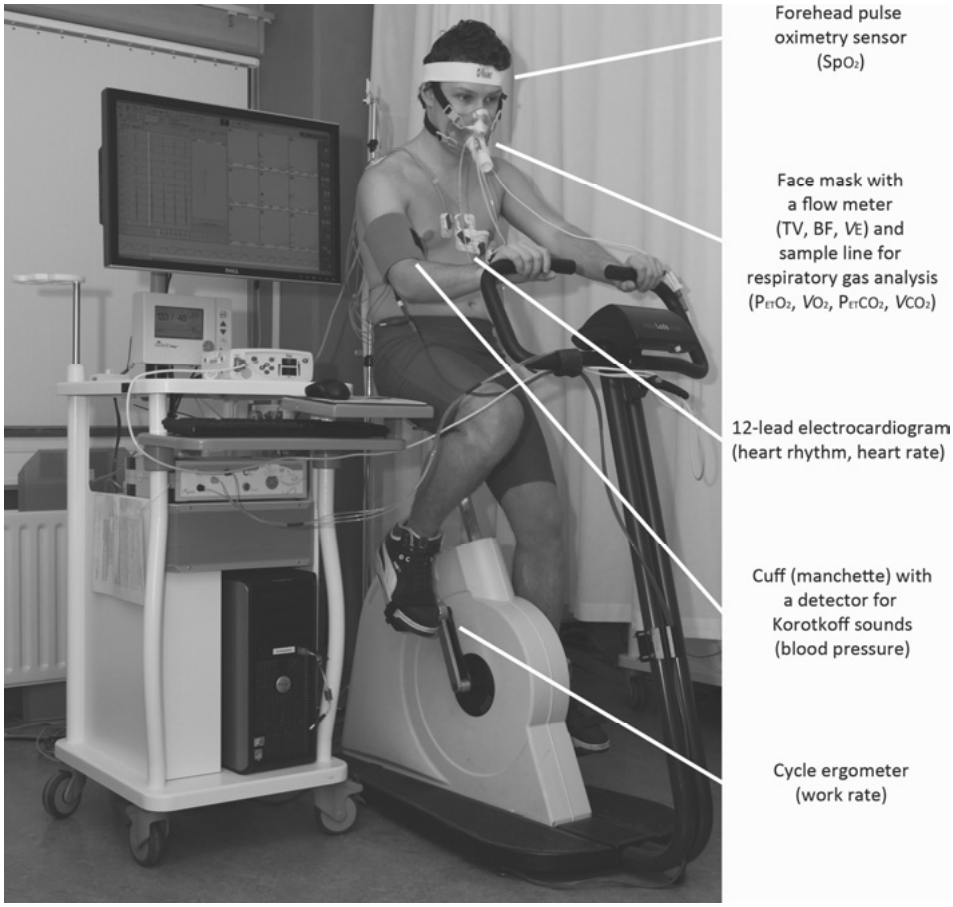
- De OUES is een valide maat voor aërobe inspanningscapaciteit die onafhankelijk is van de bereikte inspanningscapaciteit boven de ventilatoire drempel bij gezonde kinderen en bij kinderen met een congenitale hartaandoening (kinderen met een Fontan circulatie en kinderen die een operatieve correctie voor tetralogie van Fallot hebben ondergaan);
- De OUES correleert sterk met de $V\text{O}_{2\text{peak}}$ en de ventilatoire drempel in deze populaties en reflecteert de cardiopulmonale functie aan de hand van de ventilatoire efficiëntie;
- De OUES dient niet gehanteerd te worden als een vervanger van $V\text{O}_{2\text{peak}}$-metingen;
- Interpretatie van de behaalde OUES-waarden dient te geschieden op basis van een vergelijking met adequate normwaarden, een vergelijking tussen (groepen) kinderen, of longitudinale evaluaties binnen één kind;
- Het is aan te bevelen om absolute OUES-waarden te normaliseren voor lichaamsomvang bij kinderen en adolescenten, waarbij de correctie voor lichaamsoppervlakte of vetvrije massa de grote inter-individuele variatie in OUES-waarden het meest reduceert;
- Het is aan te bevelen om een kind tijdens een cardiopulmonale inspanningstest aan te moedigen om zolang mogelijk te blijven inspannen richting zijn of haar $V\text{O}_{2\text{peak}}$, om zoveel mogelijk datapunten te verkrijgen voor het berekenen van de OUES, aangezien de correlaties (met bijvoorbeeld $V\text{O}_{2\text{peak}}$ en de ventilatoire drempel) sterker worden wanneer meer datapunten gebruikt worden voor de bepaling van de OUES;
- Het is aan te bevelen om alle inspanningsdata te gebruiken voor het berekenen van de OUES, behalve wanneer een plateau in de zuurstofopname ($V\text{O}_{2\text{max}}$) bereikt is, aangezien eerdere studies aangetoond hebben dat de aanwezigheid van een plateau in de zuurstofopname de waarde van de OUES doet afnemen;
- Bij kinderen met CF lijkt de OUES van mindere waarde te zijn als een maat voor aërobe inspanningscapaciteit die onafhankelijk is van de behaalde inspanningsintensiteit, vanwege een beperkt discriminerend vermogen, de nonlineariteit gedurende het laatste deel van de maximale cardiopulmonale inspanningstest en de matige correlaties met $V\text{O}_{2\text{peak}}$ en de ventilatoire drempel.

'Steep ramp test'

- De SRT is een haalbare, betrouwbare en valide inspanningstest op een fietsergometer bij gezonde kinderen;
- De geleverde prestatie op de SRT geeft een indicatie van de aërobe inspanningscapaciteit van een kind, omdat de primaire uitkomstmaat van de SRT (WR_{peak}) sterk correleert met de behaalde VO_{2peak} tijdens een reguliere cardiopulmonale inspanningstest bij gezonde kinderen en kinderen met CF;
- Aangezien de SRT goed getolereerd wordt en cardiopulmonaal minder belastend blijkt te zijn dan de reguliere cardiopulmonale inspanningstest, kan de SRT wellicht gebruikt worden als een alternatief voor het evalueren van de inspanningscapaciteit bij minder gemotiveerde kinderen en patiënten met een ventilatoir gelimiteerde inspanningscapaciteit;
- Gebaseerd op de pediatrische normwaarden beschreven in *HOOFDSTUK 6* is het aan te bevelen om het derde percentiel als een afkappunt te gebruiken voor een beneden gemiddelde SRT prestatie;
- Aangezien de SRT niet gebruikt dient te worden als een vervanger van de reguliere cardiopulmonale inspanningstest, is het aan te bevelen om kinderen met een beneden gemiddelde SRT prestatie door te verwijzen voor een uitgebreide cardiopulmonale inspanningstest;
- De SRT kan gebruikt worden als een haalbaar alternatief voor het evalueren van de inspanningscapaciteit van een kind en kan wellicht ook gebruikt worden voor het opstellen van een individueel trainingsprogramma op een fietsergometer.

Appendix

Set-up for standard cardiopulmonary exercise testing



An adolescent performing CPET at the Child Development & Exercise Center of the Wilhelmina Children's Hospital, University Medical Center Utrecht.

ABBREVIATIONS: BF=breathing frequency; CPET=cardiopulmonary exercise testing; $P_{ET}CO_2$=partial end-tidal carbon dioxide tension; $P_{ET}O_2$=partial end-tidal oxygen tension; SpO_2=peripheral oxygen saturation; TV=tidal volume; $\dot{V}CO_2$=carbon dioxide production; $\dot{V}E$=minute ventilation; $\dot{V}O_2$=oxygen uptake.

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Acknowledgements / Dankwoord

Met het schrijven van dit dankwoord ben ik toegekomen aan het laatste onderdeel van mijn proefschrift. Het laatste onderdeel van een prachtige periode uit mijn leven waarin ik ontzettend veel geleerd heb, veel leuke nieuwe mensen heb leren kennen en veel kansen gekregen heb. Enerzijds vind ik het erg spijtig dat het na de openbare verdediging van mijn proefschrift allemaal tot een einde gekomen is, anderzijds liggen er nu weer nieuwe uitdagingen te wachten. Nieuw onderzoek, meedraaien in de kliniek en het geven van onderwijs. Ook hoop ik weer wat meer te kunnen focussen op het trainen op de fiets, iets dat ik af en toe enorm heb moeten missen. Hoewel, ik kan inmiddels stellen dat hoe meer vooruitgang ik boekte, des te meer parallellen ik ontdekte tussen promoveren en fietsen. Promoveren is als koersen. Het gaat soms bergop en soms bergaf. Het is af en toe enorm afzien. Stoempen, fietsen op karakter. Er even helemaal doorheen zitten. Met je tong op het stuur tegen de wind in harken. Jezelf compleet het snot voor de ogen rijden. Soms zelfs vloeken, tieren en schelden. Promoveren is ook af en toe geparkeerd staan. Af en toe een gat dichtrijden. Weleens in de chasse patate zitten. Hongerklop krijgen. Sommige onderzoekers gebruiken doping tijdens het promoveren. Sommigen moeten lossen en héél af en toe lees je achter de naam van een promovendus het Franse woord '*abandon*'… Het afronden van mijn proefschrift voelde dan ook als solo met je handen in de lucht over de finish uitbollen in de Koninginne-etappe. Samenvattend bevat promoveren alle ingrediënten voor een spectaculaire koers, met enorm veel verhalen, anekdotes, dramatiek, heroïek en romantiek. Promoveren is buitengewoon gaaf, maar net als koersen schrijf je een proefschrift niet in je eentje, dat doe je samen. Het is onmogelijk om een ieder die mij op enige wijze gesteund heeft in de afgelopen jaren hieronder apart te noemen. Daarom wil ik hierbij iedereen bedanken voor de gegeven steun, de getoonde interesse of de geboden afleiding. Enkele belangrijke mensen wil ik in het bijzonder bedanken.

Prof.dr. P.J.M. Helders, beste Paul, ik wil je bedanken voor jouw vertrouwen in mij. Met de stage die ik in 2009 bij het Kinderbewegingscentrum in het Wilhelmina Kinderziekenhuis (WKZ), Universitair Medisch Centrum (UMC) Utrecht liep, sloot ik niet alleen mijn studie Bewegingswetenschappen aan de Universiteit Maastricht af, maar werd door jou ook de deur naar een promotietraject op een kier gezet. Mede door jouw sterke visie en de daarmee gepaard gaande effectiviteit, waren na enkele korte gesprekken de eerste grote lijnen van een promotietraject al geschetst. Sindsdien behield je altijd het overzicht als promotor en ook na jouw emiraat kon ik altijd bij je terecht en beantwoordde je mijn e-mails vlot. Dit alles zorgde voor rust. '*Bedaank veur alles!*'

Dr. T. Takken, beste Tim, ik had simpelweg geen betere co-promotor kunnen wensen. Wat een ongelofelijk respect en bewondering heb ik voor jou. De enorme parate kennis die jij hebt op het gebied van de inspanningsfysiologie en de snelheid waarmee je e-mails beantwoord en conceptartikelen voorziet van suggesties zijn ongekend. Hierdoor blink jij uit in effectiviteit, ondanks het feit dat je betrokken bent bij ontzettend veel verschillende onderzoeksprojecten. Ook dank voor de introductie in de klinische inspanningsfysiologie, iets dat ik erg waardevol vind en ontzettend graag doe. Vooral de cardiologie poli op de dinsdagochtend met jou en de kindercardioloog zijn enorm interessant, waardoor ik weet dat ik bij deze groep patiënten graag verder onderzoek wil doen in de toekomst. Ook dank ik je voor het vertrouwen om mij als docent te introduceren binnen de afstudeerrichting Fysiotherapiewetenschap van de opleiding Klinische Gezondheidswetenschappen van de Universiteit Utrecht. Het feit dat we de passie voor het wegwielrennen delen zorgde ervoor dat we ook leuke discussies hadden die niet direct werkgerelateerd waren.

Dr. S.I. de Vries, beste Sanne, ik ben erg verheugd met het feit dat ook jij mijn co-promotor bent. Ik ben je erg dankbaar voor het feit dat jij in de weekenden écht de tijd nam om delen van mijn proefschrift door te spitten en van gedetailleerd commentaar te voorzien. Jouw commentaren hebben mij aan het denken gezet en ik heb hier ontzettend veel van geleerd.

Dr. J. van der Net, beste Janjaap, nadat prof.dr. P.J.M. Helders in 2010 met emiraat ging, werd jij afdelingshoofd van het Kinderbewegingscentrum in het WKZ, UMC Utrecht. Sindsdien ben jij betrokken geraakt bij mijn promotieonderzoek. Ik heb dit als zeer plezierig ervaren. Het oplossingsgericht denken was zeer waardevol voor het onderzoek beschreven in het tweede deel van dit proefschrift. Ik kon te allen tijde jouw kamer binnenlopen en ik vond het prettig dat we af en toe het onderzoek en mijn overige activiteiten binnen het Kinderbewegingscentrum op een rij zetten en evalueerden, om vervolgens nieuwe doelen op te stellen. Ik ben bovendien ontzettend opgetogen over het feit dat ik dit jaar als postdoctoraal onderzoeker nog op jouw afdeling werkzaam ben. Ik hoop dat we onze samenwerking nog een hele poos kunnen continueren.

Dr. H.J. Hulzebos, beste Erik, jij was mijn begeleider vanuit het Kinderbewegingscentrum in het WKZ, UMC Utrecht, toen ik daar in 2009 mijn afstudeerstage volbracht. Vanzelfsprekend ben jij dan ook veel betrokken geweest bij mijn promotieonderzoek. Ik bewonder de manier waarop jij aan de hand van het klinisch redeneren een (statistisch) significante bijdrage hebt geleverd aan de hoofdstukken van mijn proefschrift. Jouw enthousiasme wat betreft de klinische inspanningsfysiologie en het daaraan gerelateerde onderzoek werkt inspirerend. Voeg, naast de vele

serieuze gesprekken, jouw gevoel voor humor, de woordgrappen en de wijsheden daaraan toe, en je weet hoeveel we ook gelachen hebben.

Dr. M. van Brussel, beste Marco, ik vind het gaaf dat jij in de oppositie zit bij de openbare verdediging van mijn proefschrift. Jij hebt mij in eerste instantie wegwijs gemaakt in de klinische inspanningsfysiologie door me mee te nemen naar inspanningstesten in het WKZ, UMC Utrecht. Ik wil je bedanken voor je mentorschap, wat zich uitte in een uitstekende samenwerking op vele gebieden. Zo heb jij qua onderzoek bijgedragen aan enkele hoofdstukken van mijn proefschrift en voeren we momenteel samen een studie uit bij rolstoelgebonden kinderen met osteogenesis imperfecta. Bovendien werken we, mede dankzij jou, sinds september 2012 samen in het onderwijs bij de afstudeerrichting Fysiotherapiewetenschap van de studie Klinische Gezondheidswetenschappen aan de Universiteit Utrecht. Tot slot dank ik je voor de interesse in de voortgang van mijn promotieonderzoek en voor je talloze goede tips en adviezen. Sinds zes maanden zijn we kamergenoten. Op onze kamer kunnen we nieuwe ideeën bespreken voor onderzoek, het onderwijs en de kliniek. Ik hoop nog veel met jou te mogen samenwerken in de toekomst.

De nog niet eerder genoemde co-auteurs van de manuscripten wil ik bedanken voor de uitstekende samenwerking. Drs. M. Akkerman, beste Moniek, tegelijkertijd deden wij onderzoek tijdens onze afstudeerstage voor de studie Bewegingswetenschappen bij het Kinderbewegingscentrum van het WKZ, UMC Utrecht. Jij vanuit de Rijksuniversiteit Groningen en ik vanuit de Universiteit Maastricht. Het manuscript waaraan wij in die periode samen gewerkt hebben is het eerste artikel in mijn proefschrift. Het waren mijn eerste echte stappen in het wetenschappelijk onderzoek. Terwijl ik na de studie Bewegingswetenschappen ging promoveren, koos jij ervoor om Fysiotherapie te gaan studeren en nu sta jij zelf ook aan de start van een promotietraject. Ik wens je veel succes en plezier toe. Dr. H.G.M. Arets, beste Bert, ik wil je bedanken voor jouw hulp bij het schrijven van de manuscripten waarin kinderen met cystische fibrose onderzocht zijn. Jouw suggesties waren altijd zeer nuttig. Verder was jij erg geïnteresseerd in de vorderingen van mijn proefschrift en bovendien altijd beschikbaar om vragen te beantwoorden. Hopelijk kunnen we in de toekomst de samenwerking continueren. Drs. A.C. Blank, beste Christian, dank voor de introductie in de kindercardiologie. Ondanks het feit dat je het ontzettend druk had in de kliniek en met je eigen onderzoek, maakte je altijd even tijd om een elektrocardiogram of een congenitale hartaandoening met mij te bespreken. Zelf ben je ook bijna klaar met je promotieonderzoek. Ik wens je veel succes met de data-analyse en ik hoop nog veel met jou samen te kunnen werken. Prof.dr. S. van Buuren, beste Stef, ik wil je bedanken voor de snelle en uitstekende service wat betreft het construeren van de referentiecurven voor de geleverde prestatie op de 'steep ramp test'. Drs. J. Obeid, dear Joyce, I want to thank you for your help with

the accelerometer analyses, as well as for your detailed suggestions for the manuscript. Furthermore, I want to thank you, your supervisor dr. Brian Timmons, and your colleagues for showing me the scientific research conducted at the Child Health & Exercise Medicine Program of McMaster University and McMaster Children's Hospital in Hamilton, Ontario, Canada. Good luck with finishing your thesis! Drs. M.S. Werkman, beste Maarten, wat hebben wij veel bij elkaar gezeten om de respons ten aanzien van inspanning bij kinderen met cystische fibrose te bespreken. Ik heb dit altijd als zeer nuttig ervaren. Ik wil je bovendien bedanken voor de snelheid waarmee je manuscripten van suggesties voorzag. Ook jij bent bijna klaar met je promotieonderzoek. Ik wens je veel succes met de afronding hiervan.

De leden van de beoordelingscommissie, prof.dr. A.J. van Vught (voorzitter), prof.dr. E.E.S. Nieuwenhuis, prof.dr. C.K. van der Ent, prof.dr. M.A. Vos en prof.dr. C.A. Williams dank ik voor het kritisch toetsen van mijn proefschrift ten aanzien van de eisen die aan een promotie gesteld worden. Prof.dr. C.A. Williams, thank you for assessing the quality of my thesis. It is a great honour that you are one of the opponents during the public defence of my thesis in Utrecht.

Dorus Gevers en Maarten Werkman, ik ervaar het als een eer dat jullie op deze belangrijke dag mijn paranimfen willen zijn. Dorus, samen hebben wij het eerste jaar van de studie Gezondheidswetenschappen aan de Universiteit Maastricht doorlopen. Uiteindelijk koos jij voor de richting Gezondheidsvoorlichting en –bevordering en ik voor de richting Bewegingswetenschappen. Desalniettemin zijn we altijd goede vrienden gebleven. Momenteel zit jij in een promotietraject bij de Universiteit Maastricht en iedere dag kruisen wij elkaar ergens op het spoor bij Weert. Jij reist namelijk per trein vanuit Oss naar Maastricht en weer van Maastricht naar Oss, terwijl ik vanuit Maastricht naar Utrecht reis, en weer terug. Op de saaie momenten in de trein is het goed om te weten dat je niet de enige langeafstandsreiziger bent. Ik wens je ontzettend veel succes met jouw verdere promotieonderzoek en hoop dat onze vriendschap nog lang mag duren. Maarten, zoals al eerder gezegd hebben wij veel samengewerkt. We hebben samen gediscussieerd, samen aan manuscripten gewerkt en elkaar geholpen met het uitvoeren van inspanningstesten. Ik hoop nog meer onderzoek met jou te kunnen doen.

Mijn collegae van het Kinderbewegingscentrum, WKZ, UMC Utrecht, ben ik zeer erkentelijk voor de stimulerende en uitdagende werkomgeving. Ik wil beginnen met het bedanken van het hart van de afdeling, het secretariaat, bemand (eigenlijk bevrouwd) door Sonja Raaff, Carla van Rooijen en Annemiek Apeldoorn. Dank voor alle hulp, zoals onder andere het aannemen van telefoongesprekken en het opzoeken van artikelen. Verder ben ik veel dank verschuldigd aan ons afdelingshoofd, dr. Janjaap van der Net, alsmede aan mijn collegae van de medische fysiologie, te

weten dr. Tim Takken, dr. Erik Hulzebos en dr. Marco van Brussel. Dr. Jeroen Jeneson, dank voor de erg interessante introductie in het meten van het spiermetabolisme tijdens inspanning. De medepromovendi drs. Maarten Werkman, drs. Rogier de Knikker, drs. Mirjam Kruijsen, drs. Johannes Noordstar en drs. Esther Habers, alsook de inmiddels gepromoveerden, dr. Janke de Groot, dr. Wim Groen en dr. Jacqueline Nuysink, dank ik voor de leerzame gedachtewisselingen en interessante discussies op velerlei gebieden. Dit geldt uiteraard ook voor mijn collegae van de kinderfysiotherapie en kinderergotherapie, dr. Ron van Empelen, dr. Marja Schoenmakers, Rian Eijsermans, drs. Lianne Verhage, drs. Patrick van der Torre, drs. Maaike Sprong, drs. Bart Bartels en Marcel Verkaart: bedankt voor alles! Met name het wekelijkse Fysiologenoverleg en de wekelijkse Teamactiviteit waren erg leerzaam en inspirerend. Marcel, dank voor je kundige hulp bij het optimaliseren van de foto's. Naast het werk hebben we een aantal supergave sportieve uitjes gehad om nooit te vergeten, waaronder een lang weekend mountainbiken in de Belgische Ardennen in 2010, het fietsen van de toertocht Liège-Bastogne-Liège in 2011, het rijden van een ijskoude, maar óh zo mooie Holland's Venetië Tocht in 2012 en een prachtige skireis in het Oostenrijkse Sölden in 2012. Tot slot waren de vele bowlingavonden met de heren in Utrecht, waarbij op hoog niveau gestreden werd om de '*Cup met de Grote Oren*', simpelweg ongekend.

Mijn collegae van de opleiding Klinische Gezondheidswetenschappen van de Universiteit Utrecht, afstudeerrichting Fysiotherapiewetenschap, te weten prof.dr. Robert Wagenaar †, dr. Janjaap van der Net, dr. Tim Takken, dr. Marco van Brussel, dr. Caroline Speksnijder, dr. Martijn Pisters, drs. Mirelle Stukstette en drs. Rogier de Knikker, wil ik ook bedanken voor hun interesse in het verloop van mijn proefschrift. Ik ben erg blij dat ik binnen jullie team de kans heb gekregen om in het onderwijs mee te draaien. Het is een erg leuke afwisseling en bovendien ontzettend leerzaam. Ik hoop dan ook nog lang met jullie te mogen samenwerken.

Natuurlijk wil ik alle deelnemers aan de studies bedanken voor hun tomeloze inzet. Zonder hen was dit proefschrift er überhaupt nooit gekomen. Fantastisch!

De studenten die geholpen hebben met het verzamelen van normaalwaarden beschreven in hoofdstuk 5 ben ik ook veel dank verschuldigd. Beste drs. Anouk Schouten, het was een plezier om met zo een gedreven iemand samen te werken. Ik wens jou dan ook veel succes in je verdere carrière. Beste Mark Mulder, jou ken ik al heel wat langer dan vandaag. Daarom was ik ook zeer verheugd dat jij als student mee wilde helpen bij deze studie. Ik denk met veel voldoening terug aan de meetdagen waarop we 's ochtends om 05:00 uur vanuit Zuid-Limburg naar Utrecht reisden, om vervolgens waanzinnige testdagen te draaien waarbij we om 23:00 's avonds de laatste metingen verricht hadden. Na maar liefst 17 inspanningstesten

zaten we dan aan een lekker glas Duvel. Ik vond het leuk om je tijdens deze stageperiode te begeleiden en ik wens je alle geluk met je verdere studieplannen.

De longfunctieanalisten Rolien Bekkema, Joyce Tersmette, Valesca van Maanen en Hetty Faber van het Cystic Fibrosis Centrum, WKZ, UMC Utrecht, wil ik bedanken voor de deskundige adviezen met betrekking tot de meetprotocollen voor de verschillende longfunctietesten, alsook voor het mogen lenen van de meetapparatuur.

Basisschool Lucas Galecop te Nieuwegein (Otto Staal), het Cals College te Nieuwegein (Arno Pauw), het Graaf Huyn College te Geleen (Jan Willem Hamers), het Wellantcollege te Gorinchem (Bert Vreeswijk) en de Hogeschool Zuyd te Heerlen (opleiding Fysiotherapie: Monique van den Broek, opleiding Biometrie: Ludo van Etten) wil ik bedanken voor de zeer plezierige en efficiënte samenwerking. Hierdoor bleek het meten van een relatief grote groep gezonde kinderen en adolescenten voor hoofdstuk 5 achteraf gezien best mee te vallen.

De financiers van de studies beschreven in dit proefschrift, te weten Stichting BIO Kinderrevalidatie, het Wetenschappelijk College Fysiotherapie van het Koninklijk Nederlands Genootschap voor Fysiotherapie en het opleidingsfonds UMC Utrecht, ben ik zeer erkentelijk. Hetzelfde geldt voor de organisaties die zo vriendelijk waren om een deel van de drukkosten van mijn proefschrift te sponsoren. De divisie Kinderen van het UMC Utrecht, Utrecht, Lode BV, Groningen, ProCare BV, Groningen, Samcon BVBA, Merelbeke (B), bedankt voor jullie interesse in dit proefschrift en de financiële steun.

De Nederlandse Spoorwegen (NS) ben ik ook veel dank verschuldigd. Een simpele rekensom laat zien dat ik met de NS, gedurende mijn promotietraject van 1 januari 2010 tot 23 april 2013, ruim 171.000 km gereisd heb, gelijk aan ruim 4,25 keer de equatoriale omtrek van de aarde (40.075 km). Het eerste jaar van mijn promotieonderzoek tussen 's Hertogenbosch en Utrecht, en het restant van mijn promotieonderzoek (2,33 jaar) tussen Maastricht en Utrecht. Hierbij heb ik rekening gehouden met vier forensdagen per week, vakantiedagen en feestdagen. Dit betekent dat ik 1.760 uur, of ruim 73 hele dagen, in de intercity heb doorgebracht. Met de ruim 100 uur vertraging gedurende mijn promotietraject er bij opgeteld zelfs 1.860 uur, ruim 77 hele dagen. Ondanks alle negatieve verhalen over de NS, had ik met de auto waarschijnlijk veel meer vertraging ondervonden ten gevolge van files. Bovendien kon ik de trein prima werken, de krant lezen en slapen. Ik kan me geen prettigere manier van forenzen bedenken.

Ik ben mij er terdege van bewust dat ik af en toe te weinig aandacht heb kunnen geven aan mijn familie, schoonfamilie en vrienden, zeker gedurende het afgelopen

jaar. Bedankt voor jullie interesse in het onderzoek dat ik deed gedurende mijn periode als promovendus. Dat heb ik erg gewaardeerd. Ook bedankt voor de grote verscheidenheid aan sociale en sportieve uitjes. Mark Mulder, Jorrit Janssen, Imco Janssen en Niels Elgersma, dank voor de velen uren die we op de schaats gereden hebben. Komende winter hoop ik weer aan te haken. Freek Veldman, de marathon van Luxemburg zal voor altijd in mijn geheugen gegrift staan. Ik heb nu weer ruimte om een volgende uitdaging aan te gaan. De fietsgroep uit Geleen bedank ik voor de gesprekken op de fiets, de gezellige pauzes tussendoor, de epo achteraf, maar vooral voor de prachtige routes door de heuvels van Zuid-Limburg, de Voerstreek en de Ardennen.

Ik wil mijn schoonouders Henk en Ingrid bedanken voor hun interesse in mijn werkzaamheden, de heerlijke diners, glazen vino en gezellige avonden.

Mijn broers Tim en Jop en hun vriendinnen, Jolien en Tessa, wil ik bedanken voor hun interesse, alsook voor hun geduld wanneer het bij pap en mam weer over mijn promotieonderzoek ging. Tim, bedankt voor de vele tochten in de heuvels op de mountainbike. Hierdoor kon ik af en toe mijn energie kwijt. Het was telkens een welkome afleiding. Ook dank voor het in gang zetten van enkele kleinschalige wijnproeverijen en het dineren op sterrenniveau! Jop, bedankt voor de gezellige praatjes en verhalen die jij altijd hebt. Ik wens jou veel succes met jouw muziekcarrière. Ook bedankt dat jij jezelf beschikbaar stelde voor de foto in de appendix van mijn proefschrift.

Pap en mam, ik wil jullie bedanken voor de kansen die ik gekregen heb om te sporten en te studeren. Door mij te stimuleren om voor het hoogst haalbare te gaan, sta ik nu hier. Ik ben erg trots dat ik jullie nu het eindresultaat kan laten zien. Dank voor alles!

Tot slot kom ik dan uit bij de belangrijkste persoon uit mijn leven. Lieve Joyce, ik wil je bedanken voor je onvoorwaardelijke steun en vertrouwen. Ook jij hebt mij altijd gestimuleerd om voor het hoogst haalbare te gaan, ondanks het feit dat ik daarvoor 's ochtends vroeg vertrok naar Utrecht en 's avonds pas weer laat thuis was. Jij stond altijd achter me en regelde alles thuis, waaronder het overgrote deel van het huishouden en onze sociale contacten. Daarnaast zette jijzelf ook grote stappen voor jouw carrière, iets waar ik ontzettend trots op ben. Je hebt ook veel werk voor mijn proefschrift verricht, door als '*personal proofreader*' tig keren stukken tekst en manuscripten te corrigeren wat betreft het gebruik van de Engelse taal. Tussendoor hamerde jij er gelukkig ook op dat er meer in het leven was dan promoveren. Genieten bijvoorbeeld. Samen leuke dingen doen. Ik heb ongelofelijk veel zin in de rest van ons leven!

Curriculum vitae

Bart Chateau Bongers was born on October 25, 1985 in Geleen, Limburg, the Netherlands. After completing his higher general secondary education at Sint Maartens College in Maastricht, he started with the study Biometry at Zuyd University of Applied Sciences in Heerlen in 2003 (head: A.E.J. Welter, M.Sc.). In 2007, he acquired his bachelor degree. Directly hereafter, he started to study Health Sciences at Maastricht University. During the first study year, he also successfully completed a methodological and statistical course at the same institution, by which he was able to start his master Movement Sciences with a specialization in the Biology of Human Performance and Health in 2008 (head: dr. H.H.C.M. Savelberg, M.Sc., Ph.D.). His fascination for clinical exercise physiology was confirmed during his five-month research internship supervised by prof.dr. H. Kuipers, M.D., Ph.D. and dr. E. van Breda, M.Sc., Ph.D. (Department of Movement Sciences, Maastricht University) at the Child Development & Exercise Center (head: prof.dr. P.J.M. Helders, P.T., PCS, M.Sc., Ph.D.) of the Wilhelmina Children's Hospital, University Medical Center (UMC) Utrecht. After graduating with distinction at Maastricht University in 2009, a doctoral program was outlined with dr. T. Takken, M.Sc., Ph.D. in the first months of 2010 at the Child Development & Exercise Center (head: prof.dr. P.J.M. Helders, P.T., PCS, M.Sc., Ph.D., currently: dr. J. van der Net, P.T., PCS, Ph.D.) of the Wilhelmina Children's Hospital, UMC Utrecht. The scientific research he conducted throughout this period is described in this dissertation. Next to performing research activities, funding from the educational foundation of the UMC Utrecht made it possible that he was trained as a medical physiologist, specialized in clinical exercise physiology, under direct supervision of dr. T. Takken, M.Sc., Ph.D. With the gained clinical expertise and his dissertation, he hopes to complete his registration as a medical physiologist in 2013. At the moment, he continues his scientific research activities as a postdoctoral research fellow at the Child Development & Exercise Center (head: dr. J. van der Net, P.T., PCS, Ph.D.) of the Wilhelmina Children's Hospital, UMC Utrecht. Furthermore, he is involved in the care of patients and he is a university teacher at Clinical Health Sciences, specialization Physiotherapy Science, Faculty of Medicine, Utrecht University. Since 2009, Bart is happily married to Joyce. Together they live in Maastricht, in the lovely hills of the southern part of Limburg. Next to being a big fan of road cycling, he actively practices this sport himself.

Curriculum vitae

Bart Chateau Bongers werd geboren op 25 oktober 1985 te Geleen, Limburg. Na zijn middelbare schoolperiode doorlopen te hebben op het Sint Maartens College te Maastricht, startte hij in 2003 met de opleiding Biometrie aan de Hogeschool Zuyd te Heerlen (hoofd: drs. A.E.J. Welter). In 2007 behaalde hij zijn bachelordiploma. Aansluitend startte hij met de studie Gezondheidswetenschappen aan de Universiteit Maastricht. Gedurende het eerste studiejaar volgde hij tevens een cursus methodologie en statistiek aan diezelfde instelling, zodat hij in 2008 direct kon beginnen aan de master Bewegingswetenschappen, met als specialisatierichting 'Biology of Human Performance and Health' (hoofd: dr. H.H.C.M. Savelberg). Zijn fascinatie voor de klinische inspanningsfysiologie werd bevestigd tijdens zijn wetenschappelijke onderzoeksstage van vijf maanden gesuperviseerd door prof.dr. H. Kuipers en dr. E. van Breda (Vakgroep Bewegingswetenschappen, Universiteit Maastricht) bij het Kinderbewegingscentrum (hoofd: prof.dr. P.J.M. Helders) van het Wilhelmina Kinderziekenhuis (WKZ), Universitair Medisch Centrum (UMC) Utrecht. Na cum laude zijn bul te hebben behaald in 2009 aan de Universiteit Maastricht, werd in samenwerking met dr. T. Takken begin 2010 een promotietraject opgezet bij het Kinderbewegingscentrum van het WKZ, UMC Utrecht (hoofd: prof.dr. P.J.M. Helders, thans: dr. J. van der Net). Het wetenschappelijk onderzoek dat hij gedurende deze periode heeft verricht, is beschreven in deze dissertatie. Naast onderzoekswerkzaamheden is hij door financiering vanuit het opleidingsfonds UMC Utrecht in staat gesteld om onder directe supervisie van dr. T. Takken opgeleid te worden tot medisch fysioloog, met als specialisatie klinische inspanningsfysiologie. Met de opgedane klinische ervaring en zijn dissertatie, hoopt hij in 2013 de registratie tot medisch fysioloog (Stichting voor opleiding tot Medisch-Biologisch Wetenschappelijk Onderzoeker, SMBWO) af te ronden. Momenteel continueert hij zijn wetenschappelijke onderzoeksactiviteiten als postdoctoraal onderzoeker bij het Kinderbewegingscentrum van het WKZ, UMC Utrecht (hoofd: dr. J. van der Net). Ook is hij betrokken bij de patiëntenzorg en is hij als docent verbonden aan de opleiding Klinische Gezondheidswetenschappen, afstudeerrichting Fysiotherapiewetenschap, Faculteit Geneeskunde, Universiteit Utrecht. Bart is sinds 2009 gelukkig getrouwd met Joyce en samen wonen zij in Maastricht, te midden van de lieflijke heuvels van Zuid-Limburg. Naast fervent liefhebber van het wegwielrennen te zijn, beoefent hij deze sport ook zelf actief.

List of publications

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