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CHAPTER 8

Application of the steep ramp test for aerobic fitness testing in children with cancer

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ABSTRACT

Children with and after cancer are found to have a decreased physical fitness, frequently resulting in decreased physical functioning. The gold standard test for assessing aerobic fitness, a component of physical fitness, is the respiratory gas analyses-based cardiopulmonary exercise test (CPET). However, equipment for gas analysis is often unavailable in local physical therapy centres and non-university hospitals. The Steep Ramp Test (SRT), is a cycle ergometer test with a fast increase in workload, a short duration, and does not require respiratory gas analysis equipment.

The aim of this study was to compare the results of the CPET and the SRT, in children with cancer, and to assess whether the SRT can be used for aerobic fitness assessment in clinical practice in this population.

This study is a cross-sectional assessment using baseline data of a randomized controlled trial.

The study was performed in a hospital setting.

Sixty-one children (mean age 12.9 years; 33 boys) with cancer were included in the analysis; 16 children were on non-intensive chemotherapy treatment, 45 were in the first year thereafter.

Participants performed both the SRT and the CPET on a cycle ergometer with respiratory gas analysis. Data of the two tests were compared and regression analyses were performed.

CPET test results revealed a higher impact on the cardiovascular system, as shown by higher peak ventilation (47.8 versus 52.0 Litres per min) and peak heart rates (173 versus 191 beats per min), compared to the SRT. In addition, the test time was significantly longer (90 s versus 390 s). Yet, the primary outcome of the SRT (peak work rate) was able to reliably estimate the peak oxygen uptake of the CPET.

The peak oxygen uptake was comparable between the SRT and the CPET, although the peak work rate was significantly higher during the SRT. This study showed that the SRT is a valid instrument to assess aerobic fitness in children with cancer.

The SRT is less time consuming and can be performed without gas analysis in a non-clinical setting, making it less demanding for children.

INTRODUCTION

In a global population of 1.8 billion children, it was estimated that 175,300 new cases of cancer would occur in 2008 among children aged 0-14 years.[292] There are many types of cancer, with different treatment protocols, treatment effects and co-morbidities. However, in all children this life event and its subsequent intensive therapy have a high impact on the child.

Some specific childhood cancer treatment modalities, such as chest and craniospinal irradiation, and exposure to anthracyclines or bleomycin are known to increase the risk for cardiomyopathy and pulmonary dysfunction.[23,24,34,293,294] These late effects show a direct effect on the child's cardiopulmonary fitness[53] and have influence on its abilities to return to school, and participate in sports and social events.[34,138,171] Yet, physical exercise training, and exercise testing, during and after childhood cancer therapy can be performed safely and might help.[92,94,138,240]

The primary goal of many exercise training interventions is increasing physical fitness; a combination of aerobic fitness, muscular endurance, muscular strength, body composition and flexibility.[35] Controlled studies have investigated the effects of an exercise intervention on physical fitness in children with cancer.[63–65,76,181] However, these studies lack clarity concerning the optimal physical fitness test for both local and laboratory-based settings.[180] The best direct measurement of aerobic fitness is the peak oxygen uptake (VO_{2peak}).[103,295]

Currently, the gold standard for assessing aerobic fitness and VO_{2peak} in both healthy and chronically ill children and adults is the cardiopulmonary exercise test (CPET).[103,296] However, the CPET is a laboratory-based exercise test requiring respiratory gas exchange analysis which has two disadvantages. First, the test is relatively invasive as the expired air is collected through an uncomfortable mask or mouthpiece. Second, the equipment for gas analysis is often unavailable in local physical therapy centres and non-university hospitals, which hampers assessment of changes in aerobic fitness beyond the setting of a specialised clinic.

In addition, rehabilitation and aerobic fitness examination near home decreases the time involved for the child and family. This is an advantage for children with cancer who already have frequent hospital visits for treatment or evaluation, in addition to their school and social activities. Therefore, it is important to assess the validity of an easier and more readily available test to measure aerobic fitness in children with cancer.

There are different methods to assess aerobic fitness in children, both sub-maximal and maximal.[297] Field tests are known to be easy and often readily available. Field tests that are often used, such as the Astrand test and the six-minute walk test, assess functional capacity.[298,299] These tests are not designed to determine the peak exercise capacity and/or maximal effort and, therefore, might not serve as a valid alternative to the CPET in clinical populations.[298,300] However, the Steep Ramp Test (SRT) might be an option. The SRT is an incremental cycle ergometer test with a fast increase in workload, a short duration, and does not require respiratory gas analysis equipment. The SRT, already used in adult cancer patients to assess aerobic fitness[235], was highly correlated with the CPET in adults and had good test-retest reliability [intra-class correlation coefficient peak work rate (WR_{peak}) 0.996; *P*-value < 0.001][235]**.** Using a regression equation, the SRT can reliably estimate peak oxygen uptake.[301] Also in healthy children, the SRT has shown to be a reliable and valid test when compared with the CPET.[302] However, to our knowledge, the reliability and validity of the SRT has not yet been assessed in paediatric cancer patients. In children with cancer the validity of the SRT can be different from healthy[302], or cystic fibrosis children[301,303] because of their changes in body composition (higher percentage of fat mass, lower muscle mass), potential mitochondrial dysfunction, and muscle weakness[28,240,216]. But above all, after a long period of hospitalization, children with cancer are in need for community-based cancer rehabilitation which requires a non-sophisticated and valid aerobic fitness testing with a low burden. Therefore, this study aims to compare the SRT with the CPET in children with cancer to assess whether the SRT is reliable for aerobic fitness testing in the paediatric cancer population. This study is performed within the framework of an ongoing randomised controlled trial (RCT) called the Quality of Life In Motion study (QLIM), which investigates the effects of a combined physical and psychosocial training program on physical fitness, muscle strength, body composition and various psychosocial outcomes for children with cancer. The design and details of this RCT have been described elsewhere.[148]

PATIENTS AND METHODS

Patients were recruited from four university medical centres: VU University Medical Center and the Academic Medical Centre (both in Amsterdam), the University Medical Center Utrecht (in Utrecht) and Erasmus Medical Center (in Rotterdam). The trial was approved by medical ethics committees of these four centres. Medical ethics committees including chairperson, protocol number and acceptance date are: i) VU university Medical Center; S.G. Bakkum, protocol number 2008/208 approved 2009 January 28; ii) University Medical Center Utrecht; W.E. van der Voet, protocol number 09-168, approved 2009 June 22; iii) Academic Medical Centre; Y.E. Donselaar, protocol number 10/168, approved 2010 August 12; iv) Erasmus Medical Center; H.A.P. Pols, protocol number MEC-2012-124, approved 2012 March 14.

Between March 2009 and September 2013, all children with cancer (aged 8-18 years of either sex), during non-intensive treatment with chemotherapy or no longer than

12 months off chemotherapy and/or radiotherapy, were eligible for participation in the QLIM study. Exclusion criteria were: planned allogeneic stem cell transplantation during cancer treatment, growth hormone use, proven cardiomyopathy, and not being able to ride a bike and/or follow sports/test instruction. Written informed consent was obtained from the parents and also from the patients themselves when aged ≥ 12 years.

In total, 68 children with cancer participated in the QLIM study and in this assessment of the baseline data. However, because of protocol deviations in one centre, six children were excluded from the analyses and one child was not able to perform the tests due to treatment complications (Figure 8.1). None of the children in this study were excluded because of cycling inabilities.

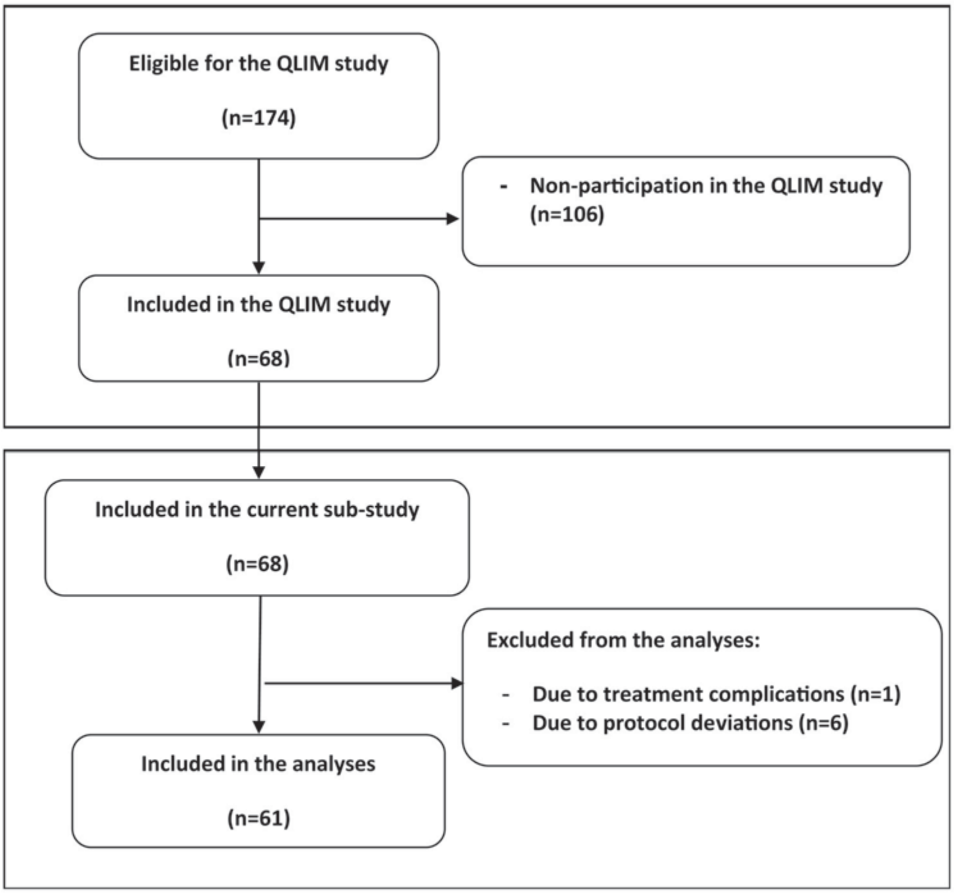


Figure 8.1 Flow chart of the QLIM study, an RCT evaluating the effects of a 12-week combined physical and psychosocial training program for children with cancer.

Finally, the study sample consisted of 61 children (33 boys and 28 girls) with a mean age of 12.9 years [3.0 standard deviation (SD)] (Table 8.1). Sixteen children were during cancer treatment; of which 12 were treated for acute lymphoblastic leukaemia (ALL) or an ALL related treatment protocol. Children had a mean height of 157.1 cm (16.7 SD) and the mean weight was 51.2 kg (16.5 SD). The mean body mass index Z-score (BMI-Z-score)[152,304] of the study group was 0.4 (1.1 SD).
Demographic data of the 106 non-participants of the QLIM study showed no significant differences from those who did participate in the RCT.[157] Non-participants had about the same age (participants 13.2 years old; non-participants 13.4 years old) and sex distribution (53% was male). In addition, a one-time survey among the non-participants (n=174; response rate 57.5%) revealed no significant differences between participants and non-participants regarding their participation in sports prior to their cancer diagnosis (83% vs. 79%, respectively).[157]

Table 8.1: Characteristics of the study participants.

Variable	Study group values (n=61) mean ± SD
Gender (female/male)	28/33
Age (years)	12.9 ± 3.0
Height (cm)	157.1 ± 16.7
Weight (kg)	51.2 ± 16.5
Body Mass Index (kg/m²)	20.1 ± 3.5
Body Mass Index Z-score	0.4 ± 1.1
FEV_1 (Liters)	2.8 ± 1.0
FEV_1 percent predicted	103.8 ± 16.7
FVC (Liters)	3.3 ± 1.3
FVC percent predicted	103.5 ± 18.9
FEV_1/FVC	85.8 ± 6.7
Diagnoses:	
Acute lymphoblastic leukaemia,	15
Acute myeloid leukaemia	7
Chronic myeloid leukaemia	1
Brain tumour	8
Hodgkin's lymphoma	9
Non-Hodgkin lymphoma	6
Rhabdomyosarcoma	3
Ewing sarcoma	4
Osteosarcoma	4
Retinoblastoma	1
Nasopharynx carcinoma	1
Hepatoblastoma	1
Wilms' tumour	1

Abbreviations: SD: standard deviation; Body mass index (kg • m²); FEV1: Forced expiratory volume in one second; FVC: forced volume vital capacity.

Measurements

During the QLIM study, measurements of physical fitness were performed on three occasions.[148] However, only the baseline measurements (performed at the start of the QLIM study, before study randomisation) were used in the current study to compare the results of the CPET and SRT. According to the study protocol of the QLIM study, the SRT was always performed before the CPET (Figure 8.2). This order was chosen because the SRT stresses the cardiopulmonary system to a lesser extent than the CPET.[305] The test protocol ensured the same time between the tests, to minimise potential bias. This was done to optimise the QLIM study design and to be able to compare the longitudinal data. Therefore, it was not possible to randomise the test order of the SRT and CPET for this baseline data-comparison.

Both the SRT and the CPET were performed on a paediatric stationary electronically braked cycle ergometer (Lode, Corival P, ProCare B.V. Groningen, the Netherlands) with gas analysis of the expired air. Ventilation and gas exchange data were determined breath-by-breath. Each child was equipped with a mouthpiece or facemask to collect the expired air. Heart rate (HR) was monitored by the use of a chest strap transmitter (Polar T31 transmitter, Polar, Kempele, Finland) or by electrocardiogram (ECG). The ECG was only used when a combination of the gas analysis and ECG monitoring was needed for cardiopulmonary data registration; this was the case for three centres. Depending on the hospital, oxygen saturation was monitored using a fingertip, earlobe, or forehead sensor connected to a pulse oximeter. Oxygen saturation was measured to control for a desaturation of the blood during the exercise test. Tests were performed with the back-up of a physician in case of an adverse event. The tests were performed between 10:00 am and 12:00 noon.

The Steep Ramp Test

During the first minute on the cycle ergometer the child was instructed to hold the paddles and asked to be silent. During this minute, the baseline cardiopulmonary parameters were obtained. The baseline assessment was followed by a warming-up period including 3 min of unloaded cycling (0 W), immediately followed by the actual SRT.

Irrespective of height, gender or age, the cycling load of the SRT increased by 25 Watt/10 s, according to the original SRT protocol.[305] The child was instructed to cycle at 60-80 rotations per minute throughout the test. Children were asked to continue cycling as long as possible; they were verbally encouraged by the assessor and researcher to do so. The peak effort was obtained when the revolutions dropped below 50 per minute, in combination with a clear inability to continue pedalling despite verbal encouragement.[305] Immediately after ending the test the recovery phase started, which consisted of 2-3 min of unloaded cycling. The obtained peak work rate ($WR_{peak,}$ in Watts), peak heart rate (HR_{peak}), total test time and the peak respiratory exchange ratio (RER_{peak}) were reported and included in the analyses.

Cardiopulmonary Exercise Test

After re-calibration of the equipment, which took approximately 5 to 10 min, the time between tests included another 3 min of passive rest. The RER had to have recovered to values within the (high) normal range (<1.0) before the start of the second test. An RER ≥ 1.0 indicates higher carbon dioxide production than oxygen uptake in the body.

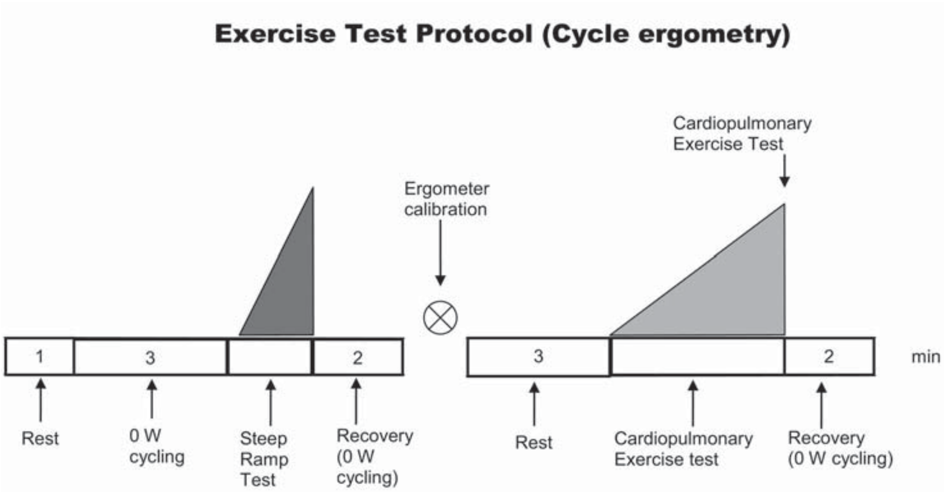


Figure 8.2 Test order of the Stereo Ramp Test and Cardiopulmonary Exercise Test during the study.

The CPET was performed according to the Godfrey protocol.[102] At the beginning of the CPET there is 3 min of baseline gas analyses without cycling, followed by 1 min of unloaded cycling. The actual test started in the fifth minute. The increase in workload depends on the child's height. For children ≤ 120 cm the workload increased with a work rate of 10 Watt per min (WR/min), for children 120-150 cm by 15 WR/min, and for children ≥ 150 cm by 20 WR/min. Children were instructed to cycle at a rate of 60-80 rotations per minute and were encouraged to continue until exhaustion. Exhaustion was defined as a drop in cadence below 50 revolutions per minute[305] in combination with hyperpnoea, facial flushing, a clear inability to continue pedalling above 60 revolutions per minute despite verbal encouragement and an HR_{peak} of at least 180 beats per minute, and/or an RER_{peak} of ≥ 1.0[102]. During the recovery or cooling down phase, the child cycled for at least 2 min without resistance (0 Watt) to recover from the test. Any problem (physical, emotional or behavioural), during or at the end of the test, were systematically recorded. In addition, each child was asked about their reason to end the test.

Mean value of the data over the last 30 s were used to calculate peak exercise values of the CPET; for the SRT the highest achieved peak scores were taken as the outcome for peak performance. Test results included: peak oxygen uptake (VO_{2peak}), peak of carbon dioxide production (VCO_{2peak}), WR_{peak}, HR_{peak}, peak ventilation (VE_{peak}) and the RER_{peak}. CPET data were included in the analyses for children that achieved a HR_{peak} of at least 180 beats per minute, and/or a RER_{peak} of ≥ 1.0.

Airway patency

Prior to the cycle ergometry, pulmonary function was assessed by spirometry, to determine whether the participant had any obstructive lung problems (such as asthma). Spirometry determines the airway patency by expiratory air flow rates and volumes using the forced expiratory volume in 1 s (FEV_1) test and forced volume vital capacity (FVC) assessment.

Statistical analysis

All statistical analyses were performed with IBM SPSS for windows version 20.0 (IBM Corp. Armonk, NY, USA). Descriptive statistical analyses were performed to describe the demographics of the study population. In case of normal distribution, the data were presented as mean (SD), otherwise as median [interquartile range (IQR)]. Bland-Altman plots were used to assess the agreement between the two tests.[306] A significant difference in the mean values between the two tests indicates that the two cycle ergometry tests are systematically producing different results.
The VO_{2peak} from CPET (L/min) was predicted using SRT WR_{peak} outcome and anthropometric characteristics (gender, height, weight, lean body mass) using linear regression (backward elimination procedure). Statistical significance was set at a *P*-value (2-sided) ≤ 0.05.

RESULTS

Twenty-one children performed the CPET with an increase workload of 15 W/min and 40 children by 20 W/min. Median FEV_1 and FVC of the children, indicative of pulmonary function, were 2.6 (IQR: 2.18-3.37) litres and 3.1 (IQR: 2.51-4.05) litres, respectively.

Baseline gas analyses, at the start of both tests, showed comparable RER and VE values. However, baseline HR values of the CPET were significantly higher ($P<0.001$) than the baseline HR values of the SRT. The mean resting HR measured before the SRT was 101 (16.4 SD), as opposed to 110 beats per minute (13.0 SD) before the CPET. During the tests, no significant abnormalities on the ECG or decrease of oxygen saturation were observed.

The results of both tests are presented in Table 8.2. The median duration of the SRT and the CPET was 90 s (1.5 min) [IQR: 61-110 s] and 390 s (6.5 min) [IQR: 300 s (5 min) – 480 s (8 min)], respectively. The standard mean difference in duration of both tests was 5.1 min (95% CI 4.6-5.6 min; *P* <0.001).

Table 8.2: Median outcome and mean difference of the Steep Ramp test and the Cardiopulmonary Exercise Test.

	SRT Median (IQR)	CPET Median (IQR)	Mean difference (95% CI)
Duration (sec)	90 (61 - 110)	390 (300 - 480)	306 (90.5; 630.8)
WR_{peak} (Watt)	200.0 (150 - 270)	122.8 (90 - 167)	-75.25 (-135.6; -10.0)
VO_{2peak} (L/min)	1.3 (0.94 - 1.86)	1.4 (1.18- 1.97)	0.12 (-0.4; 0.8)
VO_{2peak} (ml/kg/min)	26.6 (22.2 – 34.0)	29.8 (24.2 - 36.4)	2.50 (-7.1; 14.6)
VCO_{2peak} (L/min)	1.6 (1.08 - 2.30)	1.8 (1.45 - 2.41)	0.14 (-0.9; 0.9)
RER_{peak} (VCO_2/VO_2)	1.2 (1.06 - 1.37)	1.2 (1.13 - 1.25)	-0.04 (-0.5; 0.3)
VE_{peak} (L/min)	47.8 (31.4 - 66.4)	52.0 (43.5 - 77.8)	9.20 (-42.1; 54.3)
HR_{peak} (beats/min)	173 (165 – 185)	191 (182 - 196)	15.33 (-12.7; 53.5)

Abbreviations: SRT: Steep Ramp test; CPET: Cardiopulmonary Exercise Test; IQR: 25th to 75th percentile range of variation; 95% CI: 95 percent confidence interval; Sec: seconds; L/min, litres per minute; ml/kg/min, millilitres per kilogram per minute; VCO_2/VO_2: carbon dioxide production divided by oxygen uptake; WR_{peak}: peak work rate; VO_{2peak}: peak oxygen uptake; VCO_{2peak}: peak of carbon dioxide production; RER_{peak}: peak respiratory exchange ratio; VE_{peak}: peak ventilation; HR_{peak}: peak heart rate.

Bland-Altman plots were performed to present data on the mean difference between the SRT and CPET outcome variables (Figure 8.3.1, 8.3.2 and 8.3.3); the mean difference scores of the three items VO_{2peak} (L/min), VE_{peak} and HR_{peak} were above zero. This indicates that, for cardiopulmonary parameters, the CPET was more demanding than the SRT.

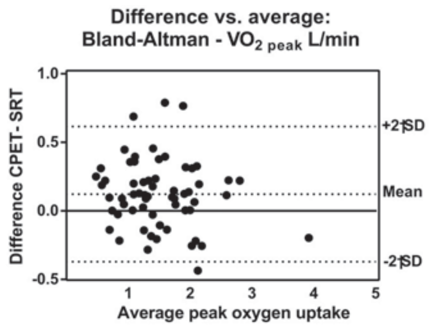
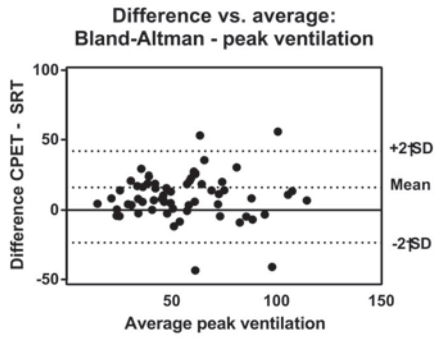
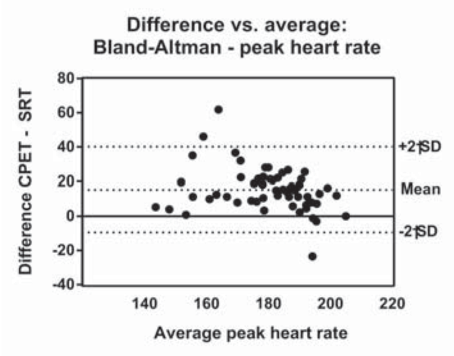


Figure 8.3 Bland-Altman plots: differences between the results of the CPET and the SRT plotted against the average of the two results.

Legend: Vs: versus; VO2peak: peak oxygen uptake; VCO2peak: peak of carbon dioxide production; RERpeak: peak respiratory exchange ratio; VEpeak: peak ventilation; HRpeak: peak heart rate





Univariate linear regression showed that SRT WR_{peak} ($P<0.001$), height ($P<0.001$), weight ($P<0.001$) and lean body mass ($P<0.001$) had a significant relationship with the CPET outcome [VO_{2peak} (L/min)]. Gender had no significant relationship with the CPET VO_{2peak} ($P=0.35$), therefore this parameter was not included in the multiple regression analyses. A backwards elimination procedure resulted in a significant model with only SRT (WR_{peak}) to predict the aerobic fitness: CPET (VO_{2peak}; L/min): CPET (VO_{2peak}; L/min) = -0.07 + 0.007 * SRT (WR_{peak}) (Figure 8.4).
The R-squared of this model showed good agreement between the two main test outcome variables ($R^2 = 0.78$).

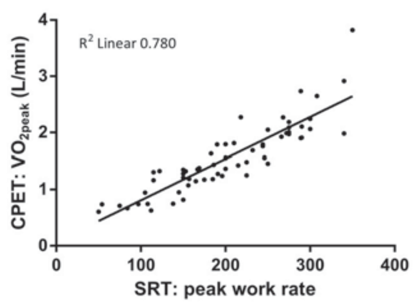


Figure 8.4: Regression line of the Cardiopulmonary Exercise Test (peak oxygen uptake in litres er minute) versus the Steep Ramp Test (peak work rate).

Related equation: CPET (L/min)= -0.07 + 0.007 * SRT (peak work rate).

N=61; standard error of the estimate = 0.292; p-value<0.001; significant deviation from zero.

Legend: CPET: Cardiopulmonary Exercise Test; SRT: Steep Ramp Test; VO2peak: peak oxygen uptake; L/min: litres per minute

DISCUSSION

The aim of this study was to assess whether the SRT can be used in clinical practice to test the aerobic fitness of children with cancer.

In adult cancer patients, rehabilitation is more or less usual care. But also in children requests for cancer rehabilitation during or shortly after treatment are becoming more frequent. In contrast to cancer treatment, physical exercise interventions are often performed in private practices or local hospitals that have no equipment to perform the CPET (that requires respiratory gas exchange analyses to accurately assess aerobic fitness). Therefore, the possibility to assess aerobic fitness, beyond the boundary of specialised clinics, is important for children with cancer.

The results of the present study show that the SRT is a short, practical exercise test which is valid to predict the aerobic fitness of children with cancer. Therefore, it may be considered a good alternative to the CPET in settings where it is not possible, or is too cumbersome, to perform the CPET.

In addition, two positive characteristics of the SRT, related to its rapid increase in workload, were found. First, children were less exhausted after the SRT compared with the longer and more demanding CPET; this was also found in a study assessing SRT and CPET results in healthy children in the Netherlands.[302] Second, related to its fast increase in Watt, the SRT represented a nice challenge for the children to obtain a high score (Watt), especially for the older children; this was less apparent during the CPET.

A serious limitation of the SRT is that it does not produce a true maximal aerobic fitness outcome, but a result which can be translated into an estimated VO_{2peak}.

In case of abnormalities an additional CPET is needed to determine the exact VO_{2peak}.

The children had lower scores on WR_{peak} compared to healthy children.[302] However in this study population, just as in healthy children, the CPET WR_{peak} score was $^1/_3$ lower than the achieved WR_{peak} of the SRT.[302] The latter study among healthy children, performed in 2013, found a mean WR_{peak} of 290 Watt during the SRT, compared to 203 Watt in our study. For the CPET the earlier study reported a mean WR_{peak} of 203 Watt in healthy children compared to 127 Watt in our population.[302]

Methodologically, it would have increased the validity of the tests comparison to perform the SRT and CPET on separate days, or to extend the time between SRT and CPET. However, during the present study, the children were not admitted to hospital and, therefore, needed to travel from home on the day of the tests; two consecutive days of exercise testing would have been too demanding. Yet, there might have been some negative influence on the HR_{peak} of the CPET because the cardiopulmonary impact of the first test was still present. Because HR is involved in reaching peak performance, there can be an effect on the peak oxygen uptake during the CPET. Whether this occurred remains unclear, but seems unlikely (or at least limited). The mean difference between the VO_{2peak} (L/min and ml/kg/min) of the SRT and CPET was non-significant, indicating a comparable outcome. Absence of an impact might be suggested by the results of another study.[301] In the latter study the CPET was performed first followed by the SRT, in a patient population consisting of children with cystic fibrosis[301] and found similar results as in the present study. Furthermore, in healthy boys it is been found that children have a very rapid recovery after high intensity exercise.[307] Therefore, additional time between the tests would probably not have had a large effect on the CPET parameters of our participants, nor on the conclusions of our study. However the possibility of a small negative effect cannot be completely excluded.

The physical impact of the SRT on the CPET could have been further assessed by including a more subjective tool such as the Borg scale. A Borg scale score of more than 18 points can be used as an indication of exhaustion, and/or a confounder for reaching peak exercise levels on the second test. Unfortunately, this assessment was not included in the study design. In addition, randomising the order of testing would have been interesting. However, due to the small number of childhood cancer patient's eligible for the study, we had to maintain the test order. Randomising the test order, or using a cross-over design, without expanding the patient inclusion, might have decreased the comparability of the longitudinal data between participants over time (QLIM study). Although, for future studies, it would be recommended to include test order randomization and possible include a prolonged rest-period between the tests.

CONCLUSION

This study shows that the SRT is a valid instrument to assess aerobic fitness in children with cancer. The oxygen uptake was comparable between the SRT and the CPET, despite that the peak work rate was significantly higher during the SRT. In contrast to the CPET, the SRT can be performed in local physical therapy practices closer to the patient's home, which reduces time, effort and costs by avoiding extra hospital visits. Overall, the SRT facilitates quicker and valid testing without the need for respiratory gas exchange analysis. The shorter duration of the test makes it less invasive, which is generally preferred, but especially in children with cancer who already face many inconvenient assessments and intensive treatment.