Criteria for the determination of maximal oxygen uptake in patients newly diagnosed with cancer: Baseline data from the randomized controlled trial of physical training and cancer (Phys-Can)

Ann Christin Helgesen Bjørke¹*, Truls Raastad¹,², Sveinung Berntsen¹

¹ Department of Sport Science and Physical Education, University of Agder, Kristiansand, Norway, ² Department of Physical Performance, Norwegian School of Sport Sciences, Oslo, Norway

* ann.c.bjorke@uia.no, ac.helgesen@hotmail.com

Abstract

Introduction
Maximal oxygen uptake ($\dot{V}O_{2\max}$) is a measure of cardiorespiratory fitness often used to monitor changes in fitness during and after treatment in cancer patients. There is, however, limited knowledge in how criteria verifying $\dot{V}O_{2\max}$ work for patients newly diagnosed with cancer. Therefore, the aim of this study was to describe the prevalence of fulfillment of typical criteria verifying $\dot{V}O_{2\max}$ and to investigate the associations between the criteria and the test leader’s evaluation whether a test was performed “to exhaustion”. An additional aim was to establish new cut-points within the associated criteria.

Methods
From the Phys-Can randomized controlled trial, 535 patients (59 ± 12 years) newly diagnosed with breast (79%), prostate (17%) or colorectal cancer (4%) performed an incremental $\dot{V}O_{2\max}$ test on a treadmill. The test was performed before starting (neo-)adjuvant treatment and an exercise intervention. Fulfillment of different cut-points within typical criteria verifying $\dot{V}O_{2\max}$ was described. The dependent key variables included in the initial bivariate analysis were achievement of a $\dot{V}O_{2\max}$ plateau, peak values for maximal heart rate, respiratory exchange ratio (RER), the patients’ rating of perceived exertion on Borg’s scale [6-20] and peak breathing frequency ($f_R$). A receiver operating characteristic analysis was performed to establish cut-points for variables associated with the test leader’s evaluation. Last, a cross-validation of the cut-points found in the receiver operating characteristic analysis was performed on a comparable sample of cancer patients (n = 80).
Results

The criteria RERpeak (<0.001), Borg’s RPE (<0.001) and $f_R$ peak ($p = 0.018$) were associated with the test leader’s evaluation of whether a test was defined as “to exhaustion”. The cut-points that best predicted the test leader’s evaluation were RER $\geq 1.14$, RPE $\geq 18$ and $f_R \geq 40$. Maximal heart rate and VO$_2$ plateau was not associated with the test leader’s evaluation.

Conclusion

We recommend a focus on RER (in the range between $\geq 1.1$ and $\geq 1.15$) and RPE ($\geq 17$ or $\geq 18$) in addition to the test leader’s evaluation. Additionally, a $f_R$ peak of $\geq 40$ breaths/min may be a cut-point to help the test leader evaluate the degree of exhaustion. However, more research is needed to verify our findings, and to investigate how these criteria will work within a population that are undergoing or finished with cancer treatment.

Introduction

A continuously increasing number of people are living with or have survived cancer [1], with most new cases occurring in persons aged 50 years and older [2]. Importantly, although improved treatment strategies have increased survival from cancer [3], most cancer treatments are collectively accompanied with negative effects on healthy cells and tissues [4–6]. Low levels of physical activity in people diagnosed with cancer [7], in combination with side effects from treatments causing injuries to the cardiovascular and muscular system [6, 8–10], are potent reasons for the clinically relevant impairments in cardiorespiratory fitness often observed in cancer treated individuals [11–14].

Patients with cancer are recommended to be as physically active as their abilities and conditions allow before, during and after cancer treatment [15, 16]. However, current exercise recommendations are rather general [17] and do not differ much for patients with cancer compared with the healthy population [18]. Based on a lack of individually tailored physical activity and exercise guidelines (e.g. frequency, intensity, type and time), second-generation trials, where specific exercise prescriptions are being investigated, are needed [19]. To be able to prescribe tailored exercise programs involving endurance training and to evaluate the effect of exercise programs, valid measurements of cardiorespiratory fitness are fundamental. One important challenge with maximal exercise tests in various patient groups, and older adults in general, is whether tests are performed with maximal effort [20]. A consequence of using submaximal test results is prescribing an exercise intensity that is too low. In addition, comparisons within (e.g. comparing different exercise intensities) and between studies is complicated if we rely on biased data [21].

When measuring cardiorespiratory fitness, direct assessment of maximal oxygen uptake ($\dot{V}O_2$max) is acknowledged as the gold standard [22]. To ensure high validity and reliability of a $\dot{V}O_2$max test (i.e. results can be reproduced), accurate instruments and experienced personnel are important [23]. Different patients and healthy individuals have various levels of experience with exercise and subjective evaluations of their effort. Furthermore, among patients with cancer, the heterogeneity may be even larger because they often are older [2], more unfit [11], and may have comorbidities and side effects like fatigue or pain [4, 24, 25]. Therefore, when assessing such a heterogenetic group of people, objective criteria to support the decision.

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whether a patient with cancer has reached her/his maximal effort (verifying $\dot{V}O_2_{\text{max}}$) is important [23].

The most widely used objective criteria, a plateau or levelling off in $\dot{V}O_2$ with increasing workload, has been extensively debated the last 20–30 years [26–31]. Variations in the number of subjects attaining a $\dot{V}O_2$ plateau are seen across studies [32], and secondary criteria are also included when verifying $\dot{V}O_2_{\text{max}}$. The term $\dot{V}O_2_{\text{peak}}$ (the highest value attained during exercise [33]) is often used when involving exercise-naïve and/or clinical populations, as there is an assumption that these persons seldom reach their highest physiologically attainable value ($\dot{V}O_2_{\text{max}}$) [33]. In the literature, estimated peak heart rate (HR), peak respiratory exchange ratio (RER), post exercise blood lactate (BLa), and self-reported Rating of Perceived Exertion (RPE) on Borg’s scale 6-20 (or other scales), with a variety of cut-points, are reported as secondary criteria to verify $\dot{V}O_2_{\text{max}}$ [34, 35]. How close these secondary criteria are associated with $\dot{V}O_2_{\text{max}}$ is not well validated. Because they all have pros and cons, the criteria and their cut-points have been discussed in the literature [23, 34–36]. Furthermore, there is no consensus on how to apply these criteria in various populations [23], but some suggestions have been made for healthy athletes [34], healthy adult subjects between 20 and 85 years [37], and for overweight or obese adults [38, 39]. It might be challenging to apply these criteria in patients newly diagnosed with cancer, and whether this population have the same physiological responses as other populations is questionable. Nevertheless, the use of well-defined objective criteria in testing newly diagnosed cancer patients is probably more important than in healthy populations because both the patient and test leader might be afraid of pushing towards maximal effort. In addition to the often-used criteria, respiratory frequency ($f_R$) has been suggested as a valid variable for defining maximal effort [40], but to our knowledge, $f_R$ has not been used as a criterion in $\dot{V}O_2_{\text{max}}$ testing. Personal experiences from test-laboratories, in which $f_R$ has been found to be useful as part of the effort-evaluation of people performing a $\dot{V}O_2_{\text{max}}$ test, is another rationale for adding this variable as a possible secondary criteria to verify $\dot{V}O_2_{\text{max}}$.

The test leader’s subjective evaluation whether a $\dot{V}O_2_{\text{max}}$ test is performed to exhaustion is important when considering the validity of $\dot{V}O_2_{\text{max}}$ tests. Although evaluations of exertion are based on predefined observations of body language and facial expressions, subjectivity is still part of the test leader’s evaluation. How test personnel give instructions and how they verbally encourage the person being tested are examples of possible biases that may affect the validity of the test results [41]. Submaximal results may occur if the test leader is inexperienced and is too “kind”; meaning that he/she does not motivate the person being tested enough, or even terminates the test before a maximal effort has been reached, of various reasons (e.g. the cancer diagnosis, comorbidities or age). Because of the aforementioned challenges of using the $\dot{V}O_2$ plateau in the evaluation of whether $\dot{V}O_2_{\text{max}}$ is reached, we are dependent on experienced and highly skilled test leaders who are able to evaluate whether a test is performed to exhaustion. In the present study we chose this somewhat experimental approach, by giving the test leaders’ evaluation of each $\dot{V}O_2_{\text{max}}$ test a focus in the statistical analyses.

To our knowledge, there are only one published study where criteria verifying $\dot{V}O_2_{\text{max}}$ have been investigated within a population of patients diagnosed with cancer [42]. Schneider et al. (2019) investigated how a supramaximal verification bout could be applied in relation to feasibility and whether it could serve as a criterion when verifying $\dot{V}O_2_{\text{max}}$ in survivors from breast and prostate cancer [42]. The present study will support researchers and test leaders in their decision concerning which secondary criteria to apply when evaluating future $\dot{V}O_2_{\text{max}}$ tests in newly diagnosed patients with breast, prostate or colorectal cancer. Presumably, not all $\dot{V}O_2_{\text{max}}$ tests in the future will be performed with an added verification bout. We present the
fulfillment of a variety of criteria with different cut-points in our sample of patients. The primary objective was to determine which of the following variables; $\dot{V}O_2$ plateau, REPeak, HPeak, Borg’s RPE and $f_r$ peak, were associated with the test leader’s subjective evaluation of whether the tests were defined as “to exhaustion”. In addition, cut-points within the associated criteria were established. A second objective was to cross-validate these cut-points in a comparable sample of patients with cancer.

**Methods**

**Design and participants**

The Phys-Can study was a multicenter randomized exercise trial with a descriptive observational study to be used for comparison [43]. For the intervention trial involving exercise, 600 adults (≥18 years) recently diagnosed with either curable breast, prostate or colorectal cancer scheduled to begin their (neo-)adjuvant therapy in Uppsala, Linköping and Malmö/Lund (Sweden) were included. Exclusion criteria were stage IIIb-IV breast cancer, inability to perform basic activities of daily living, cognitive disorders, severe psychiatric disease or other disabling conditions that might contraindicate high intensity exercise (e.g. severe heart failure, severe chronic obstructive pulmonary disease or orthopaedic conditions), treatment for an additional ongoing malignant disease, BMI $<18.5$ kg/m$^2$ or pregnancy. This main study was performed between March 2015 and November 2018. Full descriptions of the purpose, the design and enrollment of the study are presented elsewhere [43]. The observational study included 102 people following the same eligibility criteria and was performed between September 2014 and February 2015. All persons deemed as eligible by a physician/oncologist were contacted by a member of the research staff who provided verbal and written information about the study. Those who agreed to participate in the study gave their written informed consent before baseline data collection. For the purpose of the present study and analyses performed herein, 535 and 80 participants with $\dot{V}O_2$ max data at baseline (within the first week after diagnosis) were included from the intervention- and observational study, respectively. Three tests were excluded due to obvious technical issues (e.g. leakages from the face mask or technical errors), but otherwise, all available baseline $\dot{V}O_2$ max tests were included in the analyses.

The Phys-Can intervention study was approved by the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2014/249) and registered in ClinicalTrials.gov (TRN = NCT02473003, October, 2014).

**Cardiorespiratory fitness test**

The participants were told not to eat, and drink anything other than water 2 hours before the test. In addition, they were told not to perform strenuous physical activity on the test day or the day before. At the test location, height and body mass were measured to the nearest 0.5 cm and 0.1 kg, respectively, while wearing light clothes and no shoes [43].

Participants performed a continuously graded exercise test on a motorized treadmill (In Uppsala; SportsArt Fitness Tr32, Washington, USA, in Lund; Rodby RL2500E, Vänge, Sweden and in Linköping; GE T2100, Helsinki, Finland (in 2015) and Rodby RL2000, Vänge, Sweden (the remaining study period)) using a modified Balke protocol. Following a 5-min warm-up with increasing workload, participants started at 4 km/h with an inclination of 2%. The inclination increased with 2% each minute until reaching 12%, from which only the speed increased 0.5 km/h per minute until exhaustion [43]. Gas exchange data were obtained breath-by-breath, using the following different gas-analyzers: Uppsala; Viasys Vmax Encore, Care
Fusion, San Diego, USA (accepted measurement errors for O₂ analyzer: ±0.06–1%), Lund; Jaeger Oxycon Pro, CareFusion, Hoechberg, Germany (accepted measurement errors for O₂ analyzer: ±0.05%) and in Linköping; Jaeger Oxycon Pro, CareFusion, Germany, Hoechberg (until Dec 15) and Cosmed Quark CPET, Rome, Italy (accepted measurement errors for O₂ analyzer: ±0.02%) in the remaining study period. The software used was: Uppsala; Vmax Encore and Cardiosoft ECG, Version 6.7, San Diego, USA, Lund; LabManager, Jlab, CareFusion, version 5.31.0, Hoechberg, Germany and in Linköping; LabManager, Jlab, CareFusion, version 5.31.0.83, Hoechberg, Germany (in 2015) and Cosmed Quark PFT Ergo, Rome, Italy for the remaining study period. To assess the rate of perceived exertion (RPE), Borg’s scale 6-20 was applied during and at the end of the _V O₂max test [44]. Instructions in how to use this scale were given before the test.

During the test, HR was measured using a Polar RS400 HR monitor in Uppsala, a Coded Polar receiver 4208 (connected to Oxycon Pro) in Lund and a heart rate receiver in the EKG equipment (GE Healthcare, CASE GE (connected to the Oxycon Pro) and a Cosmed SZ990 receiver (connected to the Cosmed Quark CPET) in Linköping. The peak average over 5 or 15 seconds was used when presenting HRpeak. Regarding _V O₂, RER and _f_R, the highest 60 s mean of the 10-, 15- or 30 s sampling averages (acquisition time differed between the tests/labs) in the last part of the test was reported as the peak value. When describing fulfillment of different percentages of predicted HR, the Tanaka equation, 208 − (0.7 · age) was applied because this has been found to be more valid than the often-used 220 − age HRmax equation [45].

Detecting a plateau in oxygen uptake

A computer program was developed to detect whether a _V O₂ plateau or leveling off occurred during the test time. Using this program, each of the extracted excel files with the test results were processed using an algorithm based on the definition of _V O₂ plateau by Taylor and colleagues [46], where a change in _V O₂ should be less than 150 mL from one minute to the next (Δ _V O₂ ≤ 150 mL/min). Additionally, the cut-points of ≤80 ml/min and ≤50 ml/min were studied with similar definitions using the program. The highest average in _V O₂ over 1 minute was compared with the minute before or the minute after and whether _V O₂ for these time points differed ≤150 mL ≤ 80 mL and ≤50 mL. Each of these three cut-points was investigated to descriptively present the prevalence of fulfilling each cut point. In the logistic regression analysis, the cut-point of ≤150 ml/min was chosen to be included because this is believed to fit best with our test-protocol which has very small expected _V O₂ increments between each stage [46].

Test leader evaluation

After completing the tests, the test leaders were instructed to report factors related to challenges that could affect test outcomes. Additionally, each test leader reported the evaluation of every test with respect to whether the test was defined as “to exhaustion”. The evaluation was based on the observed body language, such as unsteady walking/running, bending the upper body (e.g. bending forward), facial expression showing exhaustion, hyperventilation and other signs reflecting that a maximal effort had been given. All test leaders were instructed, certified and followed up by the same person in the Phys-Can project group. A pilot-study was additionally conducted before the Phys-Can intervention study, where the predefined standards and test protocols were proven by the test leaders (and with some cancer patients).
Participant characteristics and questionnaires
Living situation, education, sick-leave, smoking status and diagnosis were retrieved through questionnaires and medical journals. The Multidimensional Fatigue Inventory (MFI) \cite{47} and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer patients (EORTC QLQ C30) \cite{48} were used to retrieve information about physical fatigue, global health status and physical function.

Physical activity monitoring
The number of hours in moderate to vigorous intensity physical activity per day was retrieved from the physical activity monitor SenseWear Armband Mini (BodyMedia Inc., Pittsburgh, PA, USA). The activity monitor was delivered on the day the $\dot{V}O_2$max test was performed. Patients were instructed to wear it for 7 consecutive days, accepting at least 4 days of registration with at least 80% wearing time each day. Physical activity registrations above 3 metabolic equivalents (METs) were defined as moderate to vigorous intensity physical activity \cite{49}.

Statistical analyses
Patient characteristics and results from the $\dot{V}O_2$peak tests were presented as mean values ± standard deviation (SD) and numbers with percentages. For descriptive purposes, the mean $\dot{V}O_2$peak within “fulfillment” and “not fulfillment” of a variety of criteria and cut-points used in the literature were presented in a figure using GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla California, USA, www.graphpad.com).

To determine associations between the criteria variables and the test leader’s evaluation, logistic regression analysis was performed using the Hosmer step-down procedure \cite{50}. The key dependent variables included in the initial bivariate analysis were achievement of a $\dot{V}O_2$ plateau, HRpeak, RERpeak, Borgs' RPEpeak and $f_R$peak. In addition, $\dot{V}O_2$peak, diagnosis, age, body mass and test time were included as adjusting variables. All variables significant at the 0.25 level were included in the final multivariate model. The odds ratios (ORs) and 95% confidence intervals (95%CIs) were calculated for 0.10 units regarding RERpeak. To investigate collinearity and interaction, pairwise correlations were performed for all the five key dependent variables in addition to $\dot{V}O_2$peak and test time. Furthermore, a receiver operating characteristic (ROC) analysis was performed to establish cut-points for variables associated with the test leader’s evaluation. These cut-points represented the point where the sensitivity and specificity were highest in correctly categorizing the test leader’s evaluation (”to exhaustion” or not). Finally, a cross-validation of the cut-points found in the ROC analysis was performed on the participants in the Phys-Can Cohort study, using a cross-table.

The analyses were performed using SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0, IBM Corp., Armonk, NY, USA) and Statistical Analysis System (SAS version 9.1.3, SAS, North Carolina, USA). The level of statistical significance was set to 0.05.

Results
Baseline characteristics of the participants in the intervention and in the cohort study are presented in Table 1. The two samples were comparable in respect to all characteristics, where mean age was 59 years and both samples included approximately 80% women with breast cancer, 15% men with prostate cancer and 4%–5% patients with colorectal cancer.
Peak values and test duration from the cardiorespiratory fitness test are given in Table 2.

The prevalence of fulfilment of the three \( \dot{V}O_2 \) plateau criteria cut-points in the intervention and cohort study were: \( \dot{V}O_2 \leq 150 \text{ ml/min} \); 90\% and 86\%, \( \dot{V}O_2 \leq 80 \text{ ml/min} \); 63\% and 65\%, and \( \dot{V}O_2 \leq 50 \text{ ml/min} \); 45\% and 53\%.

Table 2. Peak values and test-duration from the \( \dot{V}O_2 \)-max-tests performed at baseline in the Phys-Can Intervention study and the Phys-Can Cohort study, presented in mean (SD).

|                      | Phys-Can Intervention | Phys-Can Cohort |
|----------------------|-----------------------|-----------------|
| \( \dot{V}O_2 \)peak, ml/kg/min | 29.8 (7.3)            | 29.2 (7.1)      |
| HR\(_\text{peak}\), beats/min      | 166 (19)              | 168 (19)        |
| Predicted HR\(_\text{max}\), %      | 99 (9.2)              | 100 (9.6)       |
| RER\(_\text{peak}\) \( VC\text{O}_2/\dot{V}O_2 \) | 1.16 (0.10)           | 1.19 (0.11)     |
| VE\(_\text{peak}\), l/min            | 79 (20)               | 79 (19)         |
| \( f_R \)\(_\text{peak}\), breaths/min | 40 (7.8)              | 41 (6.4)        |
| Borg scale, RPE \(_{6-20}\)       | 17.9 (1.6)            | 17.0 (1.3)      |
| Test-duration, min             | 9.9 (2.8)             | 9.4 (2.6)       |

**Abbreviations:** \( \dot{V}O_2 \) = oxygen uptake; VE = ventilation. % Percentage of predicted maximal heart rate, by the Tanaka formula.
In the intervention study there were 465 (87%) and 70 (13%) tests evaluated as “to exhaustion” and “not to exhaustion”, respectively. The corresponding numbers were 76 (95%) and 4 (5%) in the cohort study. For the intervention study, VO_2peak was significantly (p<0.001) higher in the tests evaluated as “to exhaustion” (30.3 ml/kg/min, CI: 29.6–30.9) than “not to exhaustion” (26.6 ml/kg/min, CI: 24.9–28.3).

The percentage distribution and mean VO_2peak in subjects fulfilling and not fulfilling different cut-points within the criteria of VO_2 plateaux, RER, predicted HR (Tanaka) and Borgs' RPE are presented in Fig 1. Regarding the VO_2 plateau criterion, the most accessible cut-point (ΔVO_2 ≤150 ml/min) was fulfilled by nearly all patients (91%), but mean VO_2peak was the same as in patients who had not fulfilled this cut-point. The prevalence of fulfillment of cut-points was reduced by being stricter (≤80 [63%] and ≤50 ml/min [45%]), but mean VO_2peak

Fig 1. Mean (with SD) VO_2peak stratified on fulfilling and not fulfilling criteria for VO_2max in patients diagnosed with breast, prostate or colorectal cancer (n = 535). Abbreviations: RER = Respiratory Exchange Ratio; RPE = rates of perceived exertion on Borg scale 6–20; VO_2 = oxygen uptake; VCO_2 = carbon dioxide production. Tanaka, HR_{max} = 208 - (0.7·age). Plateau, ΔVO_2 = a change in VO_2 of less than 150, 80 or 50 ml/min from one minute to the next minute.

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was significantly higher \((p < 0.001\) and \(p = 0.028\), respectively) in the patients who did not fulfill these two cut-points (Fig 1). The largest difference in VO\(_2\)peak was observed between individuals who fulfilled \((n = 514; 30.1\ \text{ml/kg/min})\) and those who did not fulfill \((n = 21; 22.2\ \text{ml/kg/min})\) the RER \(\geq 1.0\) criterion \((p < 0.001)\). Many patients fulfilled the strictest cut-point of \(\geq 95\%\) predicted HRpeak \(76\%\). Regarding scoring on Borg’s scale, mean VO\(_2\)peak in “fulfilled” vs “not fulfilled” did not differ across the three cut-points.

As seen in the bivariate analysis presented in Table 3, \(f_R\) peak, HRpeak, RERpeak, peak Borg’s RPE and plateau were significantly associated with the test leader’s evaluation \((p = 0.010)\). In the multivariate analysis, peak values for \(f_R\), RER and Borg’s RPE remained significantly associated with the test leader’s evaluation \((p < 0.001)\). When adjusting for age, diagnosis, VO\(_2\)peak and test-duraiton.

### Table 3. Odds ratios (OR’s) from bivariate- and multivariate analysis with test-lead-ers’ subjective evaluation of the VO\(_2\)max test as the outcome variable.

| Effect variable | Bivariate analysis | Multivariate analysis |
|-----------------|--------------------|-----------------------|
|                 | OR’s (95% CI)      | p value               | OR’s (95% CI)      | p value               |
| \(f_R\) peak, breaths/min | 1.12 (1.07, 1.17) | <0.001               | 1.06 (1.01, 1.12) | 0.018               |
| HRpeak, beat/min          | 1.02 (1.00, 1.04) | 0.017               |                      |                       |
| RERpeak, VCO\(_2\)/VO\(_2\) | 2.21 (1.59, 3.08) | <0.001               | 2.07 (1.39, 3.08) | <0.001               |
| Borg scale, RPE \(_{6\rightarrow20}\) | 2.04 (1.68, 2.46) | <0.001               | 2.05 (1.67, 2.51) | <0.001               |
| Plateau, \(\Delta VO_2 \leq 150\ \text{ml/min}\) | 2.22 (1.01, 4.87) | 0.048               |                      |                       |

The coefficients are given with 95\% confidence intervals. Abbreviations: CI = Confidence interval; OR’s = Odds Ratio’s; \(f_R\) = respiratory frequency; HR = heart rate; RER = Respiratory Exchange Ratio; RPE = rates of perceived exertion; VCO\(_2\) = carbon dioxide production; VO\(_2\) = oxygen uptake. Adjusted for age, diagnosis, VO\(_2\)peak and test-duration.

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was significantly higher \((p<0.001\) and \(p = 0.028\), respectively) in the patients who did not fulfill these two cut-points (Fig 1). The largest difference in VO\(_2\)peak was observed between individuals who fulfilled \((n = 514; 30.1\ \text{ml/kg/min})\) and those who did not fulfill \((n = 21; 22.2\ \text{ml/kg/min})\) the RER \(\geq 1.0\) criterion \((p <0.001)\). Many patients fulfilled the strictest cut-point of \(\geq 95\%\) predicted HRpeak \(76\%\). Regarding scoring on Borg’s scale, mean VO\(_2\)peak in “fulfilled” vs “not fulfilled” did not differ across the three cut-points.

As seen in the bivariate analysis presented in Table 3, \(f_R\) peak, HRpeak, RERpeak, peak Borg’s RPE and plateau were significantly associated with the test leader’s evaluation \((p = 0.010)\). Of the four adjusting variables, test duration was the only variable that was significantly associated to the test leader’s evaluation \((p = 0.010)\). In the multivariate analysis, peak values for \(f_R\), RER and Borg’s RPE remained significantly associated with the test leader’s evaluation \((p < 0.001)\). When adjusting for age, diagnosis, VO\(_2\)peak and test duration, the probability of being categorized as “to exhaustion” was doubled both for each 0.1 increase in RER \((OR: 2.07, 95\%CI 1.39–3.08)\) and for each unit increase in Borg’s RPE \((OR: 2.05, 95\%CI 1.67–2.51)\). For each 10 breaths/min increase in \(f_R\), the probability of being categorized as “to exhaustion” was increased by 60\%.

The coefficients are given with 95\% confidence intervals. Abbreviations: CI = Confidence interval; OR’s = Odds Ratio’s; \(f_R\) = respiratory frequency; HR = heart rate; RER = Respiratory Exchange Ratio; RPE = rates of perceived exertion; VCO\(_2\) = carbon dioxide production; VO\(_2\) = oxygen uptake. Adjusted for age, diagnosis, VO\(_2\)peak and test-duration.

### Table 3. Odds ratios (OR’s) from bivariate- and multivariate analysis with test-lead-ers’ subjective evaluation of the VO\(_2\)max test as the outcome variable.

| Effect variable | Bivariate analysis | Multivariate analysis |
|-----------------|--------------------|-----------------------|
|                 | OR’s (95% CI)      | p value               | OR’s (95% CI)      | p value               |
| \(f_R\) peak, breaths/min | 1.12 (1.07, 1.17) | <0.001               | 1.06 (1.01, 1.12) | 0.018               |
| HRpeak, beat/min          | 1.02 (1.00, 1.04) | 0.017               |                      |                       |
| RERpeak, VCO\(_2\)/VO\(_2\) | 2.21 (1.59, 3.08) | <0.001               | 2.07 (1.39, 3.08) | <0.001               |
| Borg scale, RPE \(_{6\rightarrow20}\) | 2.04 (1.68, 2.46) | <0.001               | 2.05 (1.67, 2.51) | <0.001               |
| Plateau, \(\Delta VO_2 \leq 150\ \text{ml/min}\) | 2.22 (1.01, 4.87) | 0.048               |                      |                       |

The coefficients are given with 95\% confidence intervals. Abbreviations: CI = Confidence interval; OR’s = Odds Ratio’s; \(f_R\) = respiratory frequency; HR = heart rate; RER = Respiratory Exchange Ratio; RPE = rates of perceived exertion; VCO\(_2\) = carbon dioxide production; VO\(_2\) = oxygen uptake. Adjusted for age, diagnosis, VO\(_2\)peak and test-duration.

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The three cut-points for these associated criteria, calculated from the ROC curves (Fig 2), were \(f_R \geq 40\) \((true positive rate (TPR): 0.55, 95\%CI 0.51–0.60)\), RER \(\geq 1.14\) \((TPR: 0.66, 95\% CI 0.62–0.70)\) and Borg \(\geq 18\) \((TPR: 0.71, 95\% CI 0.67–0.75)\). The probabilities of correctly classifying the test leader’s evaluations were 77\% for Borg’s RPE, 73\% for RER and 70\% for \(f_R\). When combining the three criteria, the predicted probability was the best \(86\%\).

When performing the cross-validation analysis in the cohort study, three of the four \(75\%\) tests classified as “not to exhaustion” were correctly classified. Regarding the tests classified as “to exhaustion” by the test leaders, 50 of the 76 tests \(66\%\) were correctly classified. In total, \(66\%\) of the tests were correctly classified, and \(34\%\) were misclassified.

### Discussion

The criteria RERpeak, Borg’s RPE and \(f_R\) peak were associated with the test leader’s evaluation of whether a test was defined as “to exhaustion”. The cut-points that could best predict the test leader’s evaluation were RER \(\geq 1.14\), RPE \(\geq 18\) and \(f_R \geq 40\). Neither the HRmax criterion, nor attaining a VO\(_2\) plateau at the end of the VO\(_2\)max test was associated with the test leader’s evaluation.
Of note, we observed that newly diagnosed cancer patients (before beginning treatment) responded similarly to healthy age-matched individuals in peak values of $\dot{V}O_2$, RER, Borg's RPE and HR, although the present results are peak values (before applying any criteria verifying $\dot{V}O_2_{\text{max}}$) and the results from Edvardsen et al. were max values [51]. In addition, the cut-points of RER and RPE found through our ROC analysis did not differ from previously used cut-points in various populations [32, 52]. Therefore, we may assume that the cancer disease, per se, have not affected their ability to push themselves close to their maximal effort. Hence, the findings in the present study may be useful and transferable to other age-matched healthy individuals.

There is no “blueprint” regarding which outcome variable to apply when investigating criteria to verify $\dot{V}O_2_{\text{max}}$. Our experimental approach, in which the test leader’s evaluation is used for this purpose, has not been tried in this setting previously to our knowledge and is important to have in mind when interpreting our findings. Importantly, strong efforts were made in reducing the variation between test leaders through making the standards and protocols uniform for performing the tests, and all test leaders were certified by the same person who coordinated and ensured the quality of this part of the Phys-Can project.

**Respiratory exchange ratio**

The $\text{RER} \geq 1.14$ cut-point that was determined through the ROC analysis, is similar to $\geq 1.15$, which is a strict cut-point used in some studies [32], and to our knowledge, originates from the work by Issekutz et al from the 1960s [53]. In the present study, a finding of 56%
participants fulfilling the ≥1.15 criterion, was in agreement with Edvardsen and colleagues’ participants (aged 20–85 years), where 65% achieved this cut-point [37], especially when taking age into consideration. In a study of younger (mean age 37 years) overweight and obese adults, the prevalence of achieving RER≥1.15 was higher (89%) [38]. In similar treadmill protocols, RERpeak was found to decrease with age [37], and considering that our participants had a mean age of 59 years, the mean RERpeak of 1.16 in the present study was comparable to the mean RERpeak of 1.17 seen in participants from 50 to 64 years old in Edvardsen and colleagues’ study [37]. Nearly all subjects (96%) in the present study fulfilled the RER≥1.0 criterion and 91% reached the age-related recommended cut-point of RER≥1.05 for healthy individuals [37]. Schneider et al. (2019) [42] found percentage of fulfillment of the RER≥1.1 cut-point (84%) to be similar as in the present study (77%), though slightly higher, possibly because of using a cycle ergometer.

In healthy and clinical populations, the rationale for choosing one cut-point instead of another seems to be lacking, and because several cut-points have been used previously, ranging from 1.00 to 1.20 [52], the selected cut-points may have been arbitrary [35]. Explanations for why people attain different levels of RERpeak at maximal tests are not fully understood, but age may affect RERmax [37]. Another factor is the test protocol used. Because a more rapid incremental work rate increases the anaerobic energy contribution, the rate of HCO₃⁻ buffering of lactic acid-derived H⁺ ions is increased (i.e. the rate of CO₂ output will be greater because it follows the rate of H⁺ buffering) [54]. Consequently, shorter and faster test protocols result in higher RERpeak values compared with ramp tests that are of longer durations [35]. The RER cut-off values should therefore probably be made protocol specific.

Food intake and medication are also important factors that may affect RERpeak. It was suggested that habitual dietary patterns that influence the systemic acid load may account for 19% of the variability observed in RERpeak [55]. In women treated with chemotherapy and tamoxifen-like drugs, the accumulation of lactate was less compared with healthy women, especially at high exercise intensity (70% of ŔOV₉ₒ₂ max) [56]. In combination with the observed lower carbohydrate oxidation and greater fat oxidation, the authors suggested that the cancer itself, and/or the medications received, may disrupt normal energy metabolism in patients with cancer during exercise [56]. This highlights the importance of validating these criteria in different patient groups, and in cancer patients the validation should also be made in tests completed during treatment.

**Perceived exertion**

A Borg’s RPE of ≥18, found in our ROC analysis, did not differ from cut-points often seen in the literature, with observed cut-points of ≥17, ≥18 or ≥19 [52]. Congruent with our observations, 84% of participants in Edvardsen et al. (2014) achieved the most frequently used cut-point of RPE≥17. Despite close relationships between scores on Borg’s scale and physiological measures of intensity, such as HR, BLA⁺ [57], and work rate during exercise [58], the validity of Borg’s scale as a criterion in ŔOV₂₉ₒ₂ max testing has been questioned [59]. The validity in the use of this criterion depends on the subject’s understanding of the scale and associated verbal descriptors, the ability to differentiate between discomfort and physiological fatigue and motivation [60]. It has been proposed that physically inactive individuals not accustomed to exercise until exhaustion are likely to report perceived maximal exertion before they actually reach their true ŔOV₂₉ₒ₂ max [21]. The discrepancy between the percent of participants reaching RPE≥17 (86%; 30.2 ml/kg/min) and ≥18 (65%; 30.4 ml/kg/min) was large in our study, congruent with no differences in ŔOV₂₉ₒ₂ peak within fulfilling the two cut-points. Consequently, choosing an RPE≥17 cut-point would probably also work well for this patient group.
Respiratory frequency

Through the ROC analysis, ≥40 breaths/min was found to be the cut-point best associated with the test leader’s evaluation. This cut-point was reached by 52% of the participants, and these participants had a significantly (p<0.001) higher $\dot{V}O_2\text{peak}$ (32 ml/kg/min), than participants not achieving this cut-point (27 ml/kg/min). To our knowledge, $f_R$ has not been used as a criterion verifying $\dot{V}O_2\text{max}$ in previous studies, but there are implications that $f_R$ is a potentially valid measure that reflects physical effort. In two studies by Nicolo et al. [40, 61], the authors describe why $f_R$ is a better marker of physiological strain compared with the variables $\dot{V}O_2$, HR and BLA\textscript{-}. The nonlinear increase of $f_R$ during incremental exercise follows the level of acidosis from lactate production and is not affected by muscle damage or glycogen depletion, suggesting that physical effort is more causally linked with $f_R$ than BLA\textscript{-}. In addition, $f_R$ is closely related to RPE in fit males (20±3 years) and does not seem to be affected by choice of test protocol [61]. Whether $f_R$ is a valid criterion to apply as part of verifying $\dot{V}O_2\text{max}$ needs to be investigated in future studies.

Age predicted maximal heart rate

The age predicted HRmax was not significantly associated to the test leader’s evaluation of whether the test was performed “to exhaustion”. In $\dot{V}O_2\text{max}$ tests performed in different populations, fulfillment of various cut-points representing percentages of age predicted HRmax are often seen [39, 62]. Because of 10- to 12-beats-per-minute variations in HRmax in healthy individuals, even when taking age into account [63, 64], predicting HRmax is problematic [65, 66], and is likely to underestimate or overestimate HRmax on an individual level. A potentially greater variation is added in patients with cancer owing to the documented impact certain cancer treatments have on cardiac function [67], which is commonly observed as increased HR [68]. In addition, on the basis of the possible positive effects of beta-blockers (which cause lower HR or a “ceiling” in HR) in relation to cancer prognosis [69], such medications also contribute to complicating the use of this criterion. Taking these factors together, the age predicted HRmax is presumably a problematic criterion to apply in both healthy individuals [22, 39] and in patients with cancer, before, during and after cancer treatment.

Plateau in oxygen uptake

Finding as many as 91% to achieve the ≤150 ml/min plateau cut-point may be interpreted as a positive finding. However, the mean $\dot{V}O_2\text{peak}$ was the same as in the patients that did not fulfill this cut-point. Whether or not ≤150 ml/min plateau cut-point fits the participants and protocol in the present study, could be discussed. The modified Balke protocol involves very small $\dot{V}O_2$-increments from one stage to the next, and therefor seems the most suitable for the 150 ml/min cut-point, compared to the other two cut-points applied in the present study. A plateau in $\dot{V}O_2$ stands out as the most widely used criterion for verifying $\dot{V}O_2\text{max}$ [23], but some authors doubt that such a physiological plateau exists [30]. Others argue that a $\dot{V}O_2$ plateau exists, but the methodology used to identify it is central for detecting it [36]. The type of test protocol and sampling acquisition may affect the observation of a plateau [31, 32], in addition to age and fitness [23], although other studies do not agree on this [33]. Although researchers do not agree on the rationale, undoubtedly there are huge variations in the number of subjects fulfilling the plateau criterion in different studies [32]. Based on all considerations, questions are raised regarding the validity of using the plateau criterion verifying true $\dot{V}O_2\text{max}$ [70] and
other researchers have concluded that the VO₂ plateau is not a reliable physiological marker for maximal effort in all subjects [71].

**Strengths**

In a large sample of patients newly diagnosed with cancer, we have managed to elucidate criteria for validating VO₂ max tests differently from what has been previously seen in the literature. Thorough and consistent instructions and follow-up of the test leaders enabled conditions to be as similar as practically possible for all participants, independent of when or where they performed their VO₂ max tests. The test leaders were also generally experienced with exercise testing and/or with the clinical populations before the start of the Phys-Can. By including fR in our analyses, we have started to explore another possible variable as a new criterion or normative to apply in validation of VO₂ max tests.

**Limitations**

Few patients with colorectal cancer were included, so generalization to this or other nonincluded types of cancer are questionable. Furthermore, because there were only 4 of 80 (5%) VO₂ max tests evaluated as “not to exhaustion” in the cohort study, our cross-validation was more of a descriptive approach. The O₂ analyzers were from different producers across the three sites, and this may be a source of bias between the tests performed in Lund, Linköping and Uppsala. For practical reasons, validity tests were, unfortunately, not performed between the various O₂ analyzers. Measurements of Bla were not taken after the VO₂ max tests in the Phys-Can study. Although the RER value correlates highly with Bla [72], a measure of Bla would have expanded the number of objective criteria assessed. In addition, high inter-subject variability (from 5 to 17 mM) in post-exercise lactate has been reported [73] and is, accordingly, another criterion that is difficult to standardize [35]. The definition of a VO₂ plateau, as included in the present study, is perhaps not the most suitable method because of the protocol-differences between the discontinuous test protocols applied on healthy young men in the 1950s by Taylor et al. and the modified Balke protocol used in Phys-Can. In addition, we did not incorporate relative body mass into the equation. The validity of the results from the cross-validation, where a correct classification of “to exhaustion” were made in only 66% of cases from the cohort study, when applying the best three criteria can be questioned. However, the low number of tests classified as “not to exhaustion” in the cohort study makes the data figures too small to conclude anything related to how well the criteria fits another comparable sample of individuals. Last, in the present study we did not include a verification bout directly after each of the VO₂ max tests, which potentially could have been a better approach than the test leaders evaluation as the effect variable when investigating the different criteria and their cutpoints.

**Conclusions and future perspectives**

Relating the findings to clinical practice, we suggest avoiding the predicted HRmax criterion. On the basis of the observations in the present study, in addition to the complexity of detecting a VO₂ plateau when using different methodologies (e.g. test protocols and data acquisition) [23], we suggest not placing emphasis on this criterion either. We recommend a focus on RER (in the range between ≥1.1 and ≥1.15) and RPE (≥17 or ≥18) in addition to the test leader’s evaluation. Also, a fR peak of ≥40 breaths/min may be an additional cut-point to help the test leader evaluate the degree of exhaustion, but more research is needed to determine whether this should be used as a criterion.
A course for future investigations may be to determine whether the $f_R$ variable could be part of the criteria verifying $\dot{V}O_2\text{max}$. In addition, it would be interesting to precede with comparable methodologic approaches as in Schneider et al. (2019) [42], where a supramaximal verification bout was performed after the $\dot{V}O_2\text{max}$ test, in order to validate the initial $\dot{V}O_2\text{max}$ results, only apply the method using treadmill [20]. Also, a submaximal verification phase [36] which probably is more feasible for cancer patients, would be interesting to apply and investigate further. Whether achievement of the same $\dot{V}O_2\text{max}$ value in the verification bout is a valid criterion could be investigated together with the results from the present study, in patients in different phases of their cancer disease. In a recent study by Santa Mina et al. (2020), the authors describe their lab-experiences from testing 44 patients with cancer, in which only 14% achieved all of their $\dot{V}O_2\text{max}$ criteria, and none reached a $\dot{V}O_2$ plateau [74]. Hence, it is also important to investigate criteria for verifying $\dot{V}O_2\text{max}$ in patients that are undergoing or have finished cancer treatment, as these patients may have other responses and may have more difficulties in pushing themselves to maximal effort.

**Supporting information**

S1 Dataset. (XLSX)

**Author Contributions**

**Conceptualization:** Ann Christin Helgesen Bjørkø, Truls Raastad, Sveinung Berntsen.

**Data curation:** Ann Christin Helgesen Bjørkø.

**Formal analysis:** Ann Christin Helgesen Bjørkø, Truls Raastad, Sveinung Berntsen.

**Investigation:** Ann Christin Helgesen Bjørkø, Truls Raastad, Sveinung Berntsen.

**Methodology:** Ann Christin Helgesen Bjørkø, Truls Raastad, Sveinung Berntsen.

**Supervision:** Truls Raastad, Sveinung Berntsen.

**Writing – original draft:** Ann Christin Helgesen Bjørkø.

**Writing – review & editing:** Truls Raastad, Sveinung Berntsen.

**References**

1. Torre L.A., et al., Global Cancer Incidence and Mortality Rates and Trends—An Update. Cancer Epidemiol Biomarkers Prev, 2016. 25(1): p. 16–27. https://doi.org/10.1158/1055-9965.EPI-15-0578 PMID: 26667886

2. Siegel R.L., Miller K.D., and Jemal A., Cancer statistics, 2015. CA Cancer J Clin, 2015. 65(1): p. 5–29. https://doi.org/10.3322/caac.21254 PMID: 25559415

3. Arnold M., et al., Progress in cancer survival, mortality, and incidence in seven high-income countries 1995–2014 (ICBP SURVMARK-2): a population-based study. The Lancet Oncology, 2019. 20(11): p. 1493–1505. https://doi.org/10.1016/S1470-2045(19)30456-5 PMID: 31521509

4. Okwuosa T.M., Anzevino S., and Rao R., Cardiovascular disease in cancer survivors. Postgrad Med J, 2017. 93(1096): p. 82–90. https://doi.org/10.1136/postgradmedj-2016-134417 PMID: 28123076

5. Nguyen P.L., et al., Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol, 2015. 67(5): p. 825–36. https://doi.org/10.1016/j.eururo.2014.07.010 PMID: 25097095

6. Suter T.M. and Ewer M.S., Cancer drugs and the heart: importance and management. Eur Heart J, 2013. 34(15): p. 1102–11. https://doi.org/10.1093/eurheartj/ehs181 PMID: 22789916

7. Blanchard C.M., Courmeyra K.S., and Stein K., Cancer survivors’ adherence to lifestyle behavior recommendations and associations with health-related quality of life: results from the American Cancer
Society’s SCS-II. J Clin Oncol, 2008. 26(13): p. 2198–204. https://doi.org/10.1200/JCO.2007.14.6217 PMID: 18445845

8. Eickmeyer S.M., et al., The role and efficacy of exercise in persons with cancer. Pm & R, 2012. 4(11): p. 874–81.

9. Liu K.L., et al., Cardiovascular Toxicity of Molecular Targeted Therapy in Cancer Patients: A Double-Edged Sword. Acta Cardiol Sin, 2013. 29(4): p. 295–303. PMID: 27127271

10. Christensen J.F., Simonsen C., and Hojman P., Exercise Training in Cancer Control and Treatment. Compr Physiol, 2018. 9(1): p. 165–205. https://doi.org/10.1002/cphy.c180016 PMID: 30549018

11. Peel A.B., et al., Cardiorespiratory fitness in breast cancer patients: a call for normative values. J Am Heart Assoc, 2014. 3(1): p. e000432. https://doi.org/10.1161/JAHA.113.000432 PMID: 24419734

12. Wall B.A., et al., Maximal exercise testing of men with prostate cancer being treated with androgen deprivation therapy. Med Sci Sports Exerc, 2014. 46(12): p. 2210–5. https://doi.org/10.1249/MSS.0000000000000353 PMID: 24694745

13. Steins Bisschop C.N., et al., Cardiopulmonary exercise testing in cancer rehabilitation: a systematic review. Sports Med, 2012. 42(5): p. 367–79. https://doi.org/10.2165/11598480-0000000000000000 PMID: 22452663

14. Klassen O., et al., Cardiorespiratory fitness in breast cancer patients undergoing adjuvant therapy. Acta Oncol, 2014. 53(10): p. 1356–65. https://doi.org/10.3109/0284186X.2014.899435 PMID: 24837860

15. Rock C.L., et al., Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin, 2012. 62(4): p. 243–74. https://doi.org/10.3322/caac.21142 PMID: 22539238

16. Poole D.C. and Jones A.M., Measurement of the maximum oxygen uptake VO2max: VO2peak is no longer acceptable. J Appl Physiol (1985), 2017. 122(4): p. 997–1002.

17. Buffart L.M., et al., Evidence-based physical activity guidelines for cancer survivors: current guidelines, knowledge gaps and future research directions. Cancer Treat Rev, 2014. 40(2): p. 327–40. https://doi.org/10.1016/j.ctrv.2013.06.007 PMID: 23871124

18. Piercy K.L., et al., The Physical Activity Guidelines for Americans. Jama, 2018. 320(19): p. 2020–2028. https://doi.org/10.1001/jama.2018.14854 PMID: 30418471

19. Courneya K.S., et al., Top 10 research questions related to physical activity and cancer survivorship. Res Q Exerc Sport, 2015. 86(2): p. 107–16. https://doi.org/10.1080/02701367.2015.991265 PMID: 25629322

20. Poole D.C. and Jones A.M., Measurement of the maximum oxygen uptake VO2max: VO2peak is no longer acceptable. J Appl Physiol (1985), 2017. 122(4): p. 997–1002.

21. Magnan R.E., et al., Aerobic capacity testing with inactive individuals: the role of subjective experience. J Phys Act Health, 2013. 10(2): p. 271–9. https://doi.org/10.1123/jpah.10.2.271 PMID: 22398432

22. ACSM, ACSM’s Guidelines for Exercise Testing and Prescription. 2013: Wolters Kluwer Health.

23. Howley E.T., Bassett D.R. Jr., and Welch H.G., Criteria for maximal oxygen uptake: review and commentary. Med Sci Sports Exerc, 1995. 27(9): p. 1292–301. PMID: 8531628

24. Harrington C.B., et al., It’s Not over When it’s Over: Long-Term Symptoms in Cancer Survivors—A Systematic Review. The International Journal of Psychiatry in Medicine, 2010. 40(2): p. 163–181. https://doi.org/10.2190/PM.40.2.c PMID: 20848873

25. Roy S., et al., Comparison of Comorbid Conditions Between Cancer Survivors and Age-Matched Patients Without Cancer. Journal of clinical medicine research, 2018. 10(12): p. 911–919. https://doi.org/10.14740/jocm3617w PMID: 30425764

26. Bassett D.R. Jr. and Howley E.T., Maximal oxygen uptake: “classical” versus “contemporary” viewpoints. Med Sci Sports Exerc, 1997. 29(5): p. 591–603. https://doi.org/10.1097/00005768-199705000-00002 PMID: 9140894

27. Bergh U., Ekblom B., and Astrand P.O., Maximal oxygen uptake “classical” versus “contemporary” viewpoints. Med Sci Sports Exerc, 2000. 32(1): p. 85–8. https://doi.org/10.1097/00005768-200001000-00013 PMID: 10647533

28. Howley E.T., VO2max and the plateau—needed or not? Med Sci Sports Exerc, 2007. 39(1): p. 101–2. https://doi.org/10.1249/mss.0b013e31802dc897 PMID: 17218890

29. Noakes T.D., Maximal oxygen uptake: “classical” versus “contemporary” viewpoints: a rebuttal. Med Sci Sports Exerc, 1998. 30(9): p. 1381–98. https://doi.org/10.1097/00005768-199809000-00007 PMID: 9741607

30. Noakes T.D., Time to move beyond a brainless exercise physiology: the evidence for complex regulation of human exercise performance. Appl Physiol Nutr Metab, 2011. 36(1): p. 23–35. https://doi.org/10.1139/H10-082 PMID: 21326375
31. Pollock M.L., et al., A comparative analysis of four protocols for maximal treadmill stress testing. Am Heart J, 1976. 92(1): p. 39–46. https://doi.org/10.1016/s0002-8703(76)80401-2 PMID: 961576

32. Astorino T.A., Alterations in VOmax and the VO plateau with manipulation of sampling interval. Clin Physiol Funct Imaging, 2009. 29(1): p. 60–7. https://doi.org/10.1111/j.1475-097X.2008.00835.x PMID: 19125732

33. Day J.R., et al., The maximally attainable VO2 during exercise in humans: the peak vs. maximum issue. J Appl Physiol (1985), 2003. 95(5): p. 1901–7.

34. Midgley A.W., et al., Evaluation of true maximal oxygen uptake based on a novel set of standardized criteria. Appl Physiol Nutr Metab, 2009. 34(2): p. 115–23. https://doi.org/10.1139/H08-146 PMID: 19370041

35. Poole D.C., Wilkerson D.P., and Jones A.M., Validity of criteria for establishing maximal O2 uptake during ramp exercise tests. Eur J Appl Physiol, 2008. 102(4): p. 403–10. https://doi.org/10.1007/s00421-007-0596-3 PMID: 17968581

36. Schaun G.Z., The Maximal Oxygen Uptake Verification Phase: a Light at the End of the Tunnel? Sports medicine—open, 2017. 3(1): p. 44–44. https://doi.org/10.1186/s40798-017-0112-1 PMID: 29218470

37. Edvardsen E., Hem E., and Anderssen S.A., End criteria for reaching maximal oxygen uptake must be strict and adjusted to sex and age: a cross-sectional study. PloS one, 2014. 9(1): p. e85276–e85276. https://doi.org/10.1371/journal.pone.0085276 PMID: 24454832

38. Wood R.E., et al., Vo2max in overweight and obese adults: do they meet the threshold criteria? Med Sci Sports Exerc, 2010. 42(3): p. 470–7. https://doi.org/10.1249/MSS.0b013e3181b666ad PMID: 19952821

39. Misquita N.A., et al., Applicability of maximal oxygen consumption criteria in obese, postmenopausal women. J Womens Health Gend Based Med, 2001. 10(9): p. 879–85. https://doi.org/10.1089/152460901753285787 PMID: 11747683

40. Nicolò A., Massaroni C., and Passfield L., Respiratory Frequency during Exercise: The Neglected Physiological Measure. Frontiers in physiology, 2017. 8: p. 922–922. https://doi.org/10.3389/fphys.2017.00922 PMID: 29321742

41. Midgley A.W., Marchant D.C., and Levy A.R., A call to action towards an evidence-based approach to using verbal encouragement during maximal exercise testing. Clin Physiol Funct Imaging, 2018. 38(4): p. 547–553. https://doi.org/10.1111/cpf.12454 PMID: 28737297

42. Schneider J., et al., Do we underestimate VO2max in cancer survivors? Findings from a supramaximal verification test. Appl Physiol Nutr Metab, 2019.

43. Berntsen S., et al., Design of a randomized controlled trial of physical training and cancer (Phys-Can)—the impact of exercise intensity on cancer related fatigue, quality of life and disease outcome. BMC Cancer, 2017. 17(1): p. 218. https://doi.org/10.1186/s12885-017-3197-5 PMID: 28347291

44. Borg G.A., Psychophysical bases of perceived exertion. Med Sci Sports Exerc, 1982. 14(5): p. 377–81. PMID: 7154893

45. Tanaka H., Monahan K.D., and Seals D.R., Age-predicted maximal heart rate revisited. J Am Coll Cardiol, 2001. 37(1): p. 153–6. https://doi.org/10.1016/s0735-1097(00)01054-8 PMID: 11153730

46. Taylor H.L., Buskirk E., and Henschel A., Maximal oxygen intake as an objective measure of cardiorespiratory performance. J Appl Physiol, 1955. 8(1): p. 73–80. https://doi.org/10.1152/jappl.1955.8.1.73 PMID: 13242934

47. Smets E.M., et al., The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res, 1995. 39(3): p. 315–25. https://doi.org/10.1016/0022-3999(94)00125-o PMID: 7636775

48. Aaronson N.K., et al., The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst, 1993. 85(5): p. 365–76. https://doi.org/10.1093/jnci/85.5.365 PMID: 8433390

49. Garber C.E., et al., American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, muscular-skeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc, 2011. 43(7): p. 1334–59. https://doi.org/10.1249/MSS.0b013e318213fe6b PMID: 21694556

50. David W.H. and Stanley L., Applied Logistic Regression. 2. ed. ed. Wiley series in probability and statistics. 2000: United States: John Wiley & Sons Inc.

51. Edvardsen E., et al., Reference values for cardiorespiratory response and fitness on the treadmill in a 20- to 85-year-old population. Chest, 2013. 144(1): p. 241–8. https://doi.org/10.1378/chest.12-1458 PMID: 23287878
52. Midgley A.W., et al., Criteria for determination of maximal oxygen uptake: a brief critique and recommendations for future research. Sports Med, 2007. 37(12): p. 1019–28. https://doi.org/10.2165/00007256-200737120-00002 PMID: 18027991
53. Issekutz B., Birkhead J., N.C, and Rodahl K, Use of respiratory quotients in assessment of aerobic work capacity. Journal of Applied Physiology, 1962. 17(1): p. 47–50.
54. Whipp B.J., Physiological mechanisms dissociating pulmonary CO2 and O2 exchange dynamics during exercise in humans. Exp Physiol, 2007. 92(2): p. 347–55. https://doi.org/10.1113/expphysiol.2006.034363 PMID: 17185348
55. Niekamp K., et al., Systemic acid load from the diet affects maximal-exercise RER. Medicine and science in sports and exercise, 2012. 44(4): p. 709–715. https://doi.org/10.1249/MSS.0b013e3182366f6c PMID: 21912302
56. Tosti K.P., et al., Exercise in patients with breast cancer and healthy controls: energy substrate oxidation and blood lactate responses. Integr Cancer Ther, 2011. 10(1): p. 6–15. https://doi.org/10.1177/1534754103207600 PMID: 2147819
57. Borg G., Hassmen P., and Lagerstrom M., Perceived exertion related to heart rate and blood lactate during arm and leg exercise. Eur J Appl Physiol Occup Physiol, 1987. 56(6): p. 679–85. https://doi.org/10.1007/BF00424810 PMID: 3678222
58. Eston R., Use of ratings of perceived exertion in sports. Int J Sports Physiol Perform, 2012. 7(2): p. 175–82. https://doi.org/10.1123/ijssp.7.2.175 PMID: 22634967
59. Chen M.J., Fan X., and Moe S.T., Criterion-related validity of the Borg ratings of perceived exertion scale in healthy individuals: a meta-analysis. J Sports Sci, 2020. 21(10): p. 873–99. https://doi.org/10.1080/026404102320761787 PMID: 12430990
60. Beltz N.M., et al., Graded Exercise Testing Protocols for the Determination of VO2max: Historical Perspectives, Progress, and Future Considerations. J Sports Med (Hindawi Publ Corp), 2016. 2016: p. 3968393.
61. Nicolò A., et al., Comparing continuous and intermittent exercise: an “isoeffort” and “isotime” approach. PloS one, 2014. 9(4): p. e94990–e94990. https://doi.org/10.1371/journal.pone.0094990 PMID: 24736313
62. Mier C.M., Alexander R.P., and Mageean A.L., Achievement of VO2max criteria during a continuous graded exercise test and a verification stage performed by college athletes. J Strength Cond Res, 2012. 26(10): p. 2648–54. https://doi.org/10.1519/JSC.0b013e31823f8de9 PMID: 22076102
63. Fairbarn M.S., et al., Prediction of heart rate and oxygen uptake during incremental and maximal exercise in healthy adults. Chest, 1994. 105(5): p. 1365–9. https://doi.org/10.1378/chest.105.5.1365 PMID: 8181321
64. Panton L.B., et al., Relative heart rate, heart rate reserve, and VO2 during submaximal exercise in the elderly. J Gerontol A Biol Sci Med Sci, 1996. 51(4): p. M165–71. https://doi.org/10.1093/gerona/51a.4.m165 PMID: 8680999
65. Engels H.J., Zhu W., and Moffatt R.J., An empirical evaluation of the prediction of maximal heart rate. Res Q Exerc Sport, 1998. 69(1): p. 94–8. https://doi.org/10.1080/02701369.1998.10607673 PMID: 9532629
66. Sarzynski M.A., et al., Measured maximal heart rates compared to commonly used age-based prediction equations in the Heritage Family Study. Am J Hum Biol, 2013. 25(5): p. 695–701. https://doi.org/10.1002/ajhb.22431 PMID: 23913510
67. Moslehi J.J., Cardiovascular Toxic Effects of Targeted Cancer Therapies. N Engl J Med, 2016. 375(15): p. 1457–1467. https://doi.org/10.1056/NEJMra1100265 PMID: 27732808
68. Kirkham A.A., et al., A Longitudinal Study of the Association of Clinicial Indices of Cardiovascular Autonomic Function with Breast Cancer Treatment and Exercise Training, Oncologist, 2019. 24(2): p. 273–284. https://doi.org/10.1634/theoncologist.2018-0049 PMID: 30257888
69. Na Z., et al., The effects of beta-blocker use on cancer prognosis: a meta-analysis based on 319,006 patients. Onco Targets Ther, 2018. 11: p. 4913–4944. https://doi.org/10.2147/OTT.S167422 PMID: 30174436
70. Midgley A.W. and Carroll S., Emergence of the verification phase procedure for confirming ‘true’ VO (2max). Scand J Med Sci Sports, 2009. 19(3): p. 313–22. https://doi.org/10.1111/j.1600-0838.2009.00898.x PMID: 19422662
71. Myers J., et al., Effect of sampling on variability and plateau in oxygen uptake. J Appl Physiol (1985), 1990. 68(1): p. 404–10.
72. Solberg G., et al., Respiratory gas exchange indices for estimating the anaerobic threshold. J Sports Sci Med, 2005. 4(1): p. 29–36. PMID: 12431958
73. A.P.O.a.R. K., Textbook of work physiology: Physiological bases of exercise. 3rd ed. 1986: McGraw-Hill, New York.

74. Santa Mina D., et al., Aerobic capacity attainment and reasons for cardiopulmonary exercise test termination in people with cancer: a descriptive, retrospective analysis from a single laboratory. Support Care Cancer, 2020.