Cardiopulmonary exercise testing for the measurement of maximal oxygen uptake in people with cancer-related fatigue: a retrospective analysis

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ABSTRACT

Purpose: The measurement of cardiorespiratory fitness (maximal oxygen uptake) using a cardiopulmonary exercise test (CPET) has several applications in oncology. A recent analysis reported that in people with cancer, the vast majority of CPETs are discontinued before the attainment of a plateau in oxygen uptake ($\dot{V}O_2$) or secondary criteria. The objective of this study was to describe the attainment of a $\dot{V}O_2$ plateau and secondary criteria from CPET in a sample of people with cancer-related fatigue.

Methods: This was a retrospective analysis of data from 51 participants who completed a CPET as part of baseline testing for a clinical trial. The CPETs were conducted in a single laboratory by the same lead experimenter, using a cycle ergometer, standard ramp protocol and breath-by-breath gas analysis. The incidence of a $\dot{V}O_2$ plateau was compared for $\Delta\dot{V}O_2$ of $\leq 150 \text{ mL}\cdot\text{min}^{-1}$ and a more conservative $\Delta\dot{V}O_2$ of $\leq 50 \text{ mL}\cdot\text{min}^{-1}$. Independent groups dichotomized using the latter criterion were compared, including for the attainment of common secondary criteria for heart rate, rating of perceived exertion and the respiratory exchange ratio.

Results: A plateau in $\dot{V}O_2$ was observed in 100% of tests using a criterion of $\Delta\dot{V}O_2 \leq 150 \text{ mL}\cdot\text{min}^{-1}$, and this was reduced to 57% using a more conservative criterion of $\Delta\dot{V}O_2 \leq 50 \text{ mL}\cdot\text{min}^{-1}$. There were no differences in the attainment of secondary criteria (or any other variable) between groups dichotomized using observation of a $\dot{V}O_2$ plateau.

Conclusion: The validity of classic plateau criteria ($\Delta\dot{V}O_2 \leq 150 \text{ mL}\cdot\text{min}^{-1}$) to verify $\dot{V}O_{2\text{max}}$ in people diagnosed with cancer is questionable (100% attainment in the present study, 57% attainment with a more conservative definition of a $\dot{V}O_2$ plateau). Comparing our data with previous reports, we suggest that exercising maximally to elicit $\dot{V}O_{2\text{max}}$ may be more tolerable in this population using a standard ramp protocol, recumbent cycle ergometer and facemask.

Keywords: exercise oncology; maximal exercise test; cancer rehabilitation.

INTRODUCTION

Exercise should be part of standard care for people living with and beyond cancer [1]. The numerous benefits of exercise have been consistently demonstrated, and recent guidelines have provided exercise prescriptions for some common cancer-related health outcomes, including anxiety, depressive symptoms, and cancer-related fatigue (CRF) [2]. Randomized clinical trials continue to build evidence for exercise in under-represented tumour groups [3], as cancer prehabilitation [4], and in subsets of people with complex and long-term adverse effects, e.g. chronic CRF [5]. Alongside the benefits of exercise reported by patients, such as the ability to preserve normality and reclaim the body [6], improvements in objective physiological measures, including measures of cardiorespiratory fitness, are of interest. The criterion measure of cardiorespiratory fitness is maximal oxygen uptake ($\dot{V}O_{2\max}$) measured using a cardiopulmonary exercise test (CPET). In oncology, alongside the use of CPETs for measuring adaptations to exercise interventions [5], CPETs are used for several other purposes such as for pre-exercise participation screening [7], to evaluate the risk of adverse perioperative events [8], and to prescribe aerobic exercise intensity [2]. Understanding the measurement and interpretation of data related to $\dot{V}O_{2\max}$ testing in oncology is thus essential.

Maximal oxygen uptake is measured as a plateau in $\dot{V}O_2$ (a small or no increase in $\dot{V}O_2$ in response to an increase in work rate [6]), where a plateau demonstrates that oxygen uptake has reached an upper limit. Because a $\dot{V}O_2$ plateau is inconsistently observed in healthy participants [9] and is rare in some clinical populations [10], the term peak oxygen uptake ($\dot{V}O_{2\text{peak}}$) is commonly used [11]. $\dot{V}O_{2\text{peak}}$ may represent a physiological maximum or may be limited by the ability or motivation of the participant to reach peak exertion. Although subject to critique (e.g. [9,11]), secondary criteria for respiratory exchange ratio (RER), heart rate (HR), rating of perceived exertion (RPE) and blood lactate concentration have been used to confirm the $\dot{V}O_{2\text{peak}}$, i.e., substantiate that the peak value is indeed maximal. In a recent study, Santa Mina and colleagues [12] described the infrequent attainment of $\dot{V}O_{2\max}$ verification criteria in a sample of 44 people with cancer across 1-3 CPETs. In this study, a plateau in $\dot{V}O_2$ was assessed as a change in $\dot{V}O_2$ of $\leq 150 \text{ mL} \cdot \text{min}^{-1}$ despite an increase in work rate. This plateau criterion was introduced by Taylor et al. [13] in 1955, based on $\dot{V}O_2$ responses in healthy men aged 18-35 [13]. If this plateau was not achieved, $\dot{V}O_{2\max}$ was also considered 'verified' if any two of the common thresholds for RER, heart rate or RPE were surpassed [12]. Alongside the finding that nearly half of all tests were discontinued by participants due to equipment discomfort, only 14% of tests were verified using secondary criteria, and no test resulted in a plateau in $\dot{V}O_2$ [12]. The authors suggested that a cycle ergometer and facemask may be preferable to the treadmill and mouthpiece with headgear used in the study. Our experience conducting CPETs in people with cancer using a recumbent cycle ergometer and facemask may provide further insight on this point.

Thus, to investigate this further, we conducted a retrospective analysis of CPETs conducted in a randomized clinical trial involving an exercise intervention for chronic CRF. The primary aim of the present study was to replicate the analysis of Santa Mina et al. [12] regarding the attainment of maximal aerobic capacity in a sample of people with CRF after cancer treatment who completed a CPET on a cycle ergometer. Secondary aims were to (i) describe the attainment of a plateau response in $\dot{V}O_2$ using more conservative criteria that more closely match the definition of a $\dot{V}O_2$ plateau for our sample; and (ii) describe the attainment of secondary criteria according to several common or recommended thresholds.

METHODS

Participants

Participants were part of an ongoing prospective randomized controlled trial that is described in detail elsewhere (see ClinicalTrials.gov, NCT03049384 and [5]). Participants were aged 18-75 years and had completed curative-intent cancer treatment (≥ 3 months and ≤ 5 years from enrolment), self-identified as feeling fatigued/tired, and self-identified that the fatigue/tiredness developed at any point during the course of the disease (e.g. during the treatment phase) and had not resolved. Furthermore, participants scored ≤ 34 [14] on the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) [15,16]. Based on these eligibility criteria, all participants in the larger study were considered to have chronic CRF. Additional inclusion and exclusion criteria have been reported previously [5]. Written informed consent for all study procedures was obtained. The wider study was approved by the Health Research Ethics Board of Alberta Cancer Committee (HREBA.CC-16-10-10) and was performed according to the Declaration of Helsinki.

Laboratory Visit

The data for this analysis were collected during a single visit to the laboratory as part of a baseline assessment for the wider trial [5]. Participants completed a cancer-specific questionnaire (e.g. diagnosis, past and current treatments) and Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) and were also screened for arrhythmia and hypertension, determined during resting electrocardiography and blood pressure measurements, respectively. Continuation with the study was conditional on the screening process, and physician approval was sought at this stage where required. Otherwise, participants were cleared for participation by a Certified Exercise Physiologist (Canadian Society for Exercise Physiology). Following the measurement of stature (cm) and body mass (kg), a CPET was conducted for the measurement of $\dot{V}O_{2peak}$. All tests were conducted in a single exercise physiology laboratory by the lead author (RT) and a second exercise physiologist (CSEP-CEP) (primarily CL), both highly competent in maximal exercise testing, trained in cancer and exercise topics (Thrive Health), and certified in first aid and cardiopulmonary resuscitation. All laboratory visits commenced between 8-9 am, the maximal exercise test typically began after 60-90 min. Participants were advised

to consume breakfast 1.5 h prior to arrival at the laboratory, to arrive at the laboratory hydrated and to refrain from alcohol, caffeine and strenuous activity for the preceding 24 h. Participants were instrumented for the measurement of HR. Breath-by-breath pulmonary gas exchange and ventilation were measured using a metabolic cart, calibrated according to instructions prior to every test (Quark CPET, COSMED, Rome, Italy). A silicone rubber facemask with an anatomically contoured design was fitted (size options of extra-small to extra-large), and the headgear was adjusted for comfort. RT provided a detailed explanation of the purpose of the test and all aspects of the protocol before the facemask was positioned, including the nature of progressive exercise that the test required a 'maximal effort.' The RPE scale (Borg's RPE scale 6-20 [17]) was explained according to published instructions [18]. Participants were instructed to terminate the test early in the case of chest pain, dizziness, leg cramps and other major issues or concerns. Participants were given plenty of time to ask questions about the test. Once the mask was positioned, participants rested for 3 min before the test commenced, to allow time to acclimatize to the equipment.

The test was conducted on a custom-built recumbent ergometer, which uses an electromagnetically braked Velotron system (RacerMate Inc., Seattle, WA). Seat position was adjusted for each participant, and self-selected cadence (≥ 60 rpm) was determined in the first minute of the exercise test. The starting power output (25–50 W) and increment (8–15 W) were adjusted on an individual basis (based on a discussion about current physical activity levels, plus consideration of age and sex). The adjustments were intended to result in a test of 8–12 min duration. The power was increased at 1-min intervals until volitional termination or until cadence fell below 60 rpm for ≥ 5 seconds. Changes in cadence resulted in changes in resistance such that power output was controlled. The experimenters ended the test early if clinical test termination criteria were observed [19]. RPE and dyspnoea (Borg CR-10 scale [20]) were recorded every minute. For all cycling tests, verbal encouragement was provided by RT every 20-60 s [21]. A fingertip blood sample was collected at exercise cessation for the analysis of blood lactate (Lactate Scout⁺, EFK Diagnostics, Cardiff, UK), and participants completed a 5-10 min supervised cool down at ~25 W.

Data Analysis

The highest rolling 30-s average for absolute and relative $\dot{V}O_2$, V_E and RER were calculated, and a plateau in oxygen uptake was compared to two criteria for the final two consecutive 1-min intervals. For the comparison to Santa-Mina et al. [12], the first $\dot{V}O_2$ plateau criterion was a $\Delta\dot{V}O_2$ of ≤ 150 ml·min⁻¹ or [13] or 2.1 L·kg⁻¹·min⁻¹. The subsequent analysis investigated how many participants had an increase in $\dot{V}O_2$ that was ≤ 50 ml·min⁻¹. Although this has been used previously [22,23], it was chosen because it is both appreciably small (in line with the definition [6]) and based on the reported measurement accuracy for the Quark CPET of $\pm 2\%$ [24] since 50 ml·min⁻¹ relative to the mean $\dot{V}O_{2peak}$ reported in this study is ~3%. We also describe the attainment of secondary criteria based on those

commonly used in exercise physiology or previously used in people with cancer. Secondary criteria included: peak heart rate $\geq 95\%$ of age-predicted maximum [25]; peak heart rate ≤ 10 bpm of age-predicted maximum; RER ≥ 1.10 ; RER ≥ 1.15 ; blood lactate ≥ 6 mmol/L; blood lactate ≥ 8 mmol/L; RPE ≥ 17 ; RPE ≥ 19 [9,12]. Statistical analysis was conducted using jamovi (<https://www.jamovi.org/library.html>), an open-source graphical user interface for the R programming language [26]. We dichotomized the data into two independent groups based on a $\dot{V}O_{2\text{peak}} \Delta \leq 50 \text{ ml} \cdot \text{min}^{-1}$ or $> 50 \text{ ml} \cdot \text{min}^{-1}$ to test the hypothesis that the group who displayed a $\dot{V}O_2$ plateau would differ from the group that did not. For categorical variables (e.g. yes/no for attaining secondary criteria), Fisher's exact tests were used. Continuous variables (e.g. $\dot{V}O_{2\text{peak}}$) were compared using Student's *t*-tests. If the assumption of normality (Shapiro-Wilk test) or equality of variances (Levene's test) was violated, robust independent *t*-tests (Yuen's tests) were used. Effect sizes and their confidence intervals were also calculated. The alpha level was set at 0.05. An anonymized (i.e. reduced) data set is available at <https://osf.io/a83vd/>.

RESULTS

Data from 51 participants were included in the analysis. Participants were predominantly white (92%), female (65%) and had received treatment for breast cancer (45%). Participant characteristics are presented in Table 1. No adverse events occurred as a result of the maximal exercise tests used in the present analysis.

Table 1. Participant Characteristics

	Participants (<i>n</i> = 51)
Age, mean $\pm$ SD	54 $\pm$ 11
Age, range	21-71
Sex	
Male, <i>n</i> (%)	18 (35)
Female, <i>n</i> (%)	33 (65)
Height (cm), mean $\pm$ SD	171 $\pm$ 10
Body mass (kg), mean $\pm$ SD	82.4 $\pm$ 19.8
Body Mass Index (kg/m²), mean $\pm$ SD	28.0 $\pm$ 6.3
FACIT-F score, mean $\pm$ SD	27 $\pm$ 7
Months since treatment*, mean $\pm$ SD	24 $\pm$ 19
Cancer type	
Breast, <i>n</i> (%)	23 (45)
Haematological, <i>n</i> (%)	7 (14)
Colorectal, <i>n</i> (%)	4 (8)
Prostate, <i>n</i> (%)	4 (8)
Gynaecological, <i>n</i> (%)	3 (6)
Thyroid, <i>n</i> (%)	3 (6)
Head and Neck Cancer, <i>n</i> (%)	3 (6)
Oesophageal, <i>n</i> (%)	1 (2)
Kidney, <i>n</i> (%)	1 (2)
Bladder, <i>n</i> (%)	1 (2)
Oligodendroglioma, <i>n</i> (%)	1 (2)
Treatment received	
Surgery, <i>n</i> (%)	46 (90)
Chemotherapy, <i>n</i> (%)	29 (57)
Radiation therapy, <i>n</i> (%)	31 (61)
Hormonal therapy, <i>n</i> (%)	17 (33)
Hormonal therapy (ongoing), <i>n</i> (%)	14 (27)
Stem Cell transplant, <i>n</i> (%)	3 (6)

Months since treatment completion was calculated as the time between the most recent (i.e. last) surgery, chemotherapy treatment, radiation treatment or stem cell transplant (as relevant) and the date of the lab visit. The most recent treatment was also the final scheduled cancer treatment (except for hormonal therapy). Values may not sum to 100% due to rounding. FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue.

We found that 100% of the CPETs resulted in $\Delta\dot{V}O_2 \leq 150 \text{ mL}\cdot\text{min}^{-1}$ despite an increase in work rate. All participants reached $\dot{V}O_{2\text{max}}$ according to this definition of a plateau. In contrast, using a more conservative plateau criterion of $\Delta\dot{V}O_2 \leq 50 \text{ mL}\cdot\text{min}^{-1}$ despite an increase in work rate, 57% of CPETs resulted in a $\dot{V}O_2$ plateau. Data from the CPET is presented in Table 2. There were no significant differences reported in any variable between participants who met the $\dot{V}O_2$ plateau criteria and those who did not. Full statistical reporting for this finding is presented in Supplementary Table 1.

Table 2. Maximal exercise test, plateau criteria and secondary criteria.

	Participants (<i>n</i> = 51)	$\leq 50 \text{ mL}\cdot\text{min}^{-1}$ (<i>n</i> = 29)	$> 50 \text{ mL}\cdot\text{min}^{-1}$ (<i>n</i> = 22)
Maximal Exercise Test			
Initial power output (W), mean $\pm$ SD	26 $\pm$ 6	28 $\pm$ 8	25 $\pm$ 0
Increment ($\text{W}\cdot\text{min}^{-1}$)	11 $\pm$ 3	11 $\pm$ 3	12 $\pm$ 3
Cadence (rpm)	74 $\pm$ 6	73 $\pm$ 6	75 $\pm$ 5
Peak oxygen uptake ($\text{L}\cdot\text{min}^{-1}$), mean $\pm$ SD	1.93 $\pm$ 0.60	1.97 $\pm$ 0.68	1.88 $\pm$ 0.47
Peak oxygen uptake ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), mean $\pm$ SD	23.8 $\pm$ 5.2	24.1 $\pm$ 5.7	23.3 $\pm$ 4.5
End-exercise rating of perceived exertion (6-20), median [IQR]	19 [18-20]	19 [19-20]	19 [18-20]
End-exercise rating of perceived dyspnoea (0-10), median [IQR]	9 [7-10]	9 [7-10]	9 [7-9]
Peak heart rate (bpm), mean $\pm$ SD	160 $\pm$ 16	161 $\pm$ 15	159 $\pm$ 18
Percentage of age-predicted maximal heart rate (%), mean $\pm$ SD	92 $\pm$ 9	95 $\pm$ 8	94 $\pm$ 11
End-exercise blood lactate (mmol/L), mean $\pm$ SD	8.5 $\pm$ 3.0	8.5 $\pm$ 3.1	8.5 $\pm$ 3.1
Exercise time (min), mean $\pm$ SD	10.1 $\pm$ 3.0	10.5 $\pm$ 3.6	9.7 $\pm$ 1.9
Peak power output (W), mean $\pm$ SD	136 $\pm$ 44	138 $\pm$ 48	133 $\pm$ 40
Secondary Criteria			
Heart rate $\geq 95\%$ of age-predicted maximum, <i>n</i> (%)	21 (41)	13 (45)	8 (36)
Heart rate ≤ 10 bpm of age-predicted maximum, <i>n</i> (%)	25 (49)	16 (55)	9 (41)
Respiratory exchange ratio ≥ 1.10 , <i>n</i> (%)	38 (75)	22 (76)	16 (73)
Respiratory exchange ratio ≥ 1.15 , <i>n</i> (%)	28 (55)	16 (55)	12 (55)
Blood lactate ≥ 6 (mmol/L), <i>n</i> (%) [10]	41 (80)	23 (79)	19 (86)
Blood lactate ≥ 8 (mmol/L), <i>n</i> (%)	27 (53)	14 (48)	13 (59)
Rating of perceived exertion (6-20) ≥ 17 , <i>n</i> (%)	45 (88)	27 (93)	18 (82)
Rating of perceived exertion (6-20) ≥ 19 , <i>n</i> (%)	24 (47)	14 (48)	10 (45)
Met two verification criteria based on [12]	(32) 63	20 (69)	12 (55)

IQR, interquartile range

DISCUSSION

We found that 100% of participants with CRF after cancer treatment met $\dot{V}O_2$ plateau criteria ($\Delta\dot{V}O_2 \leq 150 \text{ mL}\cdot\text{min}^{-1}$) during a CPET performed using a standard ramp protocol on a recumbent cycle

ergometer with a facemask. However, the validity of this criterion to confirm a $\dot{V}O_2$ plateau is questionable because it does not indicate a minimal change in $\dot{V}O_2$ with an increase in work rate in this clinical population (further explained below). Using a more conservative plateau criterion ($\Delta\dot{V}O_2 \leq 50 \text{ mL}\cdot\text{min}^{-1}$) that is closer to the definition of a plateau response (i.e. a small or no increase in $\dot{V}O_2$ in response to an increase in work rate [6]), we observed a plateau response in 57% of participants. There were no differences in the attainment of secondary criteria (or any other variable) between groups dichotomized using observation of a $50 \text{ mL}\cdot\text{min}^{-1}$ $\dot{V}O_2$ plateau response.

A $\dot{V}O_2$ plateau is defined as a small or no increase in $\dot{V}O_2$ in response to an increase in work rate [13], but as Midgeley et al. emphasized [27], unless an absolute plateau is used (i.e. no increase in $\dot{V}O_2$), a plateau only indicates that the increase is below a pre-specified level. Specifically, the rate of change in the $\dot{V}O_2$ -work rate relationship has slowed, but $\dot{V}O_2$ is not necessarily maximal. The pre-specified amount of change used to define a $\dot{V}O_2$ plateau varies between studies. First, we used a standard criterion of $\Delta\dot{V}O_2 \leq 150 \text{ mL}\cdot\text{min}^{-1}$ [27] as used recently in people with cancer [12]. None of the CPETs in this previous study resulted in a plateau response, yet in our sample, 100% of CPETs resulted in a plateau response. One explanation for this may be that the increments used in Santa Mina et al. (a modified Bruce protocol [28]) are very large (e.g. from 2.7 km/h with a 5% gradient in minutes 4-6, to 4.0 km/h with a 10% gradient in minutes 7-9) and this may have contributed to the lack of $\dot{V}O_2$ plateaus, despite volitional peak being a reason for test termination in >40% of tests. This protocol may be preferred for some applications (e.g. monitoring of cardiac responses to exercise) but may not be optimal for eliciting $\dot{V}O_{2\text{max}}$ in people with cancer.

Although in the present study, 100% of CPETs resulted in a plateau response, this is not expected to occur 100% of the time in elite cyclists [29], and we consider this to be highly implausible in people with chronic CRF. The reason for this high response is that the change in $\dot{V}O_2$ is too liberal for a clinical population using a ramp protocol. We are not the first to note that the standard $\dot{V}O_2$ plateau criterion should not be used during continuous graded protocols with modern metabolic carts [9]. This criterion was introduced in 1955 by Taylor et al. [13] was based on men aged 18-35 (body mass ~70 kg based on the conversion of $150 \text{ mL}\cdot\text{min}^{-1}$ to $2.1 \text{ mL}\cdot\text{kg}^{-1}$) using Douglas bags and a discontinuous treadmill protocol across multiple days. Men aged 18-35 are neither the default human or person with cancer, and aside from other critiques about the size of the variation in $\dot{V}O_2$ that resulted in this criterion [27], there is little reason to suggest that this criterion is applicable to the present study participants or the data that prompted our analysis [12]. In clinical populations, including people with cancer, the increase in work rate between stages is likely to be much smaller than that used in the original study in healthy young men [13]. For example, the increment in power used in the present study is roughly 50% of that which would be suitable for healthy young men performing the same ramp protocol on a cycle ergometer (for the same test duration of 8-12 min). Using a ramp protocol with an increase in power of $\sim 10 \text{ W}\cdot\text{min}^{-1}$

(which was appropriate for most of our participants), it is not improbable that the increase in $\dot{V}O_2$ between stages could be $<150 \text{ mL} \cdot \text{min}^{-1}$ even during the early stages of a test. Our observation of a $\dot{V}O_2$ plateau response of 100% using $\Delta\dot{V}O_2 \leq 150 \text{ mL} \cdot \text{min}^{-1}$ and 57% using $\Delta\dot{V}O_2 \leq 50 \text{ mL} \cdot \text{min}^{-1}$ is similar to that previously reported in people diagnosed with cancer (91% and 45%, respectively) [23]. We may have observed a higher proportion of plateau responses due to some aspect of the protocol (e.g. use of a recumbent ergometer) or the comfort level of the participant to push themselves to peak exertion following a detailed explanation of the protocol (we have previously reported that participants felt supported and safe throughout the test [30]).

Maximal exercise with the measurement of pulmonary gas exchange and ventilation is not always possible or necessary, and functional tests of exercise capacity (such as the six-minute walk test) may be preferred for some applications, such as outside of strict laboratory settings. If an estimate of cardiorespiratory fitness is required, prediction equations based on the HR response to sub-maximal exercise or non-exercise models of $\dot{V}O_{2\text{max}}$ may be suitable for some applications if the inherent error is considered acceptable. However, assuming a CPET is warranted (e.g. for a gold-standard assessment of cardiorespiratory fitness), some equipment may be more tolerable in clinical oncology research [31]. People who are unfamiliar with treadmills may find increasing speeds/gradients challenging (especially in the case of balance concerns, e.g. with peripheral neuropathy [32]), and during weight-bearing activity, a mouthpiece is not always well-tolerated. Although $\dot{V}O_{2\text{peak}}$ may be lower on a treadmill vs. an ergometer [33] due to the recruitment of less muscle mass [34], this becomes less relevant if the treadmill test is terminated before peak exertion. Comparing the present findings with the recent study by Santa Mina et al. [12], where a treadmill protocol was combined with the use of a mouthpiece with supportive headgear, we suggest that early test termination may be avoided by the use of a cycle ergometer and facemask. Although we did not systematically record the reason for test termination, using the same secondary criteria as Santa Mina et al. (any two of the following: RPE $\geq 9/10$ [we used the equivalent of $\geq 18/20$], RER ≥ 1.15 , and/or HR $\geq 95\%$ of age-predicted maximum), we found that 63% of tests met this 'verification' in comparison to 14% [12]. Although this 'verification' is not an indication of $\dot{V}O_{2\text{max}}$, it does provide some evidence that most participants did not terminate the test early.

We found no differences in secondary criteria or $\dot{V}O_{2\text{peak}}$ (or any other variables of interest – see Supplementary Table 1) between participants who displayed a $\dot{V}O_2$ plateau of ($\Delta\dot{V}O_2 \geq 50 \text{ mL} \cdot \text{min}^{-1}$) and those who did not. The lack of difference in $\dot{V}O_{2\text{peak}}$ is in contrast to similar analysis using secondary criteria as evidence of $\dot{V}O_{2\text{max}}$ [12] but in line with research that used a $\dot{V}O_2$ levelling off [9]. In cancer survivors, use of secondary criteria to 'verify' $\dot{V}O_{2\text{max}}$ [12] will misclassify as many as one-third of tests, even when at least three secondary criteria are attained [35]. The usefulness of secondary criteria is, therefore, debatable in this population. We are not suggesting that a $\dot{V}O_2$ plateau is the only method to

confirm a $\dot{V}O_{2\max}$, but standard secondary criteria do not seem to discriminate when $\dot{V}O_{2\max}$ has occurred. As already highlighted, a "one-size-fits-all" approach to secondary criteria is not appropriate, particularly in older or clinical populations [9,11,35]. Recently, Bjørke et al. [23] suggested that the test leaders subjective evaluation (based on the body language and facial expressions of the participant) could be a measure of a maximal test, and found that criteria for RPE, RER and respiratory frequency were associated with the subjective evaluation. However, training, experience and appraisals of the participant are likely to differ between test leaders, and the addition of this as criteria for $\dot{V}O_{2\max}$ requires further investigation. An alternative solution is to include a supramaximal square wave "verification bout" performed after the incremental CPET, and compare the $\dot{V}O_2$ to that reached in the CPET [36]. For example, a verification phase could involve a 2-3-min cycling bout at a constant power output close to the peak achieved in the CPET, with the additional phase conducted after a short break. This method has been evaluated in healthy people of different ages and in patient populations, and when safety measures (e.g. health screening and exclusion of patients with a contraindication to maximal exercise) are taken, it is well-tolerated [37–39]. Furthermore, Schneider et al. [35] have evaluated the use of a verification bout in people with cancer and found that it was feasible and that 68% fulfilled the verification criterion (a difference between $\dot{V}O_{2\text{peak}}$ measured in the CPET and the verification bout of $<3\%$) and attained $\dot{V}O_{2\max}$ in the CPET. Future research should include a verification bout and report the association between a plateau response in $\dot{V}O_2$ and $\dot{V}O_{2\max}$ verification using this method.

Limitations

We did not systematically record the reasons for test termination. This was discussed as part of participant care during a general discussion with the participant during and after a supervised cool down (face mask removed), but notes were only made if the participant felt they were limited due to a symptom/other reason that was unrelated to general inability to continue (no reason specified when asked, or leg fatigue). This occurred three times (two did not have a $\dot{V}O_2$ plateau), and included xerostomia in a patient who had undergone radiation for head and neck cancer ($n=1$), the perception that the facemask was limiting breathing ($n=1$) and difficulty maintaining a cadence of ≥ 60 rpm from test onset (the brake was applied on our equipment below this rpm). It is not possible to determine which aspect of the test (cycle ergometer or facemask or both) resulted in increased attainment of $\dot{V}O_{2\max}$ and secondary criteria.

CONCLUSION

We found that 57% of participants with CRF after cancer treatment meet plateau criteria ($\Delta\dot{V}O_2 \leq 50$ mL $\cdot$ min $^{-1}$) for oxygen uptake during an incremental test when the equipment used does not result in early test termination due to participant discomfort. If maximal exercise testing is warranted, we recommend the use of a cycle ergometer (vs. treadmill) and facemask (vs. mouthpiece), if available. The validity of common criteria ($\Delta\dot{V}O_2 \leq 150$ mL $\cdot$ min $^{-1}$) to verify $\dot{V}O_{2\max}$ in people diagnosed with

cancer is highly questionable (and resulted in 100% attainment in the present study). Rather than using secondary criteria (which are variable), a more conservative plateau criterion and a verification bout may provide an alternative solution.

Disclosure/Conflict of Interest

This research was supported by the Canadian Cancer Society (grant #704208-1). The authors have no conflicts of interest to disclose.

Supplementary Table 1.

Group comparisons for a $\dot{V}O_2$ plateau of $\leq 50 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (Yes/No)	Total n	Test	Statistic	d_f	p value	Effect size	95% CI
Participant Characteristics							
Age (years)	51	Robust t -test	1.60	30.8	0.120	$\varepsilon = 0.32$	[0.00 - 0.67]
Gender (Male/Female)	51	Fisher's exact test	0.77	1	0.770	$\nu = 0.63$	
Body Mass Index (kg/m^2)	51	Student's t -test	-0.05	49	0.963	$d = -0.01$	[-0.93 - 0.20]
FACIT-F score	51	Robust t -test	1.13	25.7	0.270	$\varepsilon = 0.24$	[0.00 - 0.59]
Months since treatment	51	Robust t -test	1.07	31	0.293	$\varepsilon = 0.21$	[0.00 - 0.54]
Treatment received							
Surgery (Yes/No)	51	Fisher's exact test	0.87	1	1.000	$\nu = 0.21$	
Chemotherapy (Yes/No)	51	Fisher's exact test	0.44	1	0.253	$\nu = 0.20$	
Radiation therapy (Yes/No)	51	Fisher's exact test	2.19	1	0.248	$\nu = 0.19$	
Hormonal therapy (Yes/No)	51	Fisher's exact test	0.79	1	0.769	$\nu = 0.06$	
Ongoing hormonal therapy (Yes/No)	51	Fisher's exact test	1.02	1	1.000	$\nu < 0.01$	
Maximal Exercise Test							
Peak oxygen uptake ($\text{L} \cdot \text{min}^{-1}$)	51	Robust t -test	0.34	31	0.740	$\varepsilon = 0.08$	[0.00 - 0.52]
Peak oxygen uptake ($\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	51	Student's t -test	-0.53	49	0.598	$d = -0.15$	[-0.70 - 0.41]
End-exercise rating of perceived exertion (6-20)	51	Mann-Whitney U	281		0.447	$r = 0.12$	
End-exercise rating of perceived dyspnoea (0-10)	51	Mann-Whitney U	284		0.502	$r = 0.11$	
Peak heart rate (bpm)	50	Student's t -test	-0.25	48	0.803	$d = -0.07$	[-0.63 - 0.49]
Percentage of age predicted maximal heart rate (%)	50	Student's t -test	-0.99	48	0.329	$d = -0.28$	[-0.84 - 0.29]
End-exercise blood lactate (mmol/L)	51	Student's t -test	0.04	49	0.965	$d = 0.01$	[-0.54 - 0.57]
Exercise time (min)	51	Robust t -test	0.49	31	0.628	$\varepsilon = 0.10$	[0.00 - 0.54]
Peak power output (W)	51	Student's t -test	-0.35	49	0.726	$d = -0.10$	[-0.65 - 0.46]
Secondary Criteria							
Heart rate $\geq 95\%$ of age-predicted max (Yes/No)	50	Fisher's exact test	1.50	1	0.569	$\nu = 0.10$	
Heart rate ≤ 10 bpm of age-predicted max (Yes/No)	50	Fisher's exact test	1.90	1	0.393	$\nu = 0.16$	
Respiratory exchange ratio ≥ 1.10 (Yes/No)	51	Fisher's exact test	1.17	1	1.000	$\nu = 0.04$	
Respiratory exchange ratio ≥ 1.15 (Yes/No)	51	Fisher's exact test	1.03	1	1.000	$\nu < 0.01$	
Blood lactate $\geq 6 \text{ mmol}/\text{L}$ (Yes/No)	51	Fisher's exact test	0.86	1	1.000	$\nu = 0.03$	
Blood lactate $\geq 8 \text{ mmol}/\text{L}$ (Yes/No)	51	Fisher's exact test	0.65	1	0.573	$\nu = 0.11$	
Rating of perceived exertion ≥ 17 (Yes/No)	51	Fisher's exact test	2.93	1	0.383	$\nu = 0.17$	
Rating of perceived exertion ≥ 19 (Yes/No)	51	Fisher's exact test	1.12	1	1.00	$\nu = 0.28$	
Verification according to [12]	51	Fisher's exact test	1.83	1	0.383	$\nu = 0.15$	

FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; 95% CI, 95% confidence intervals for the effect size; d_f , degrees of freedom

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