

The University of Northern Colorado Cancer Rehabilitation Institute Treadmill Protocol Accurately Measures VO₂peak in Cancer Survivors

Daniel Yoon Kee Shackelford¹, Jessica Marlene Brown¹, Brent Michael Peterson², Jay Schaffer³ and Reid Hayward^{4*}

¹College of Health Sciences, Carroll University, USA

²School of Science, Technology, and Health, Biola University, USA

³Department of Applied Statistics and Research Methods, University of Northern Colorado, USA

⁴School of Sport and Exercise Science, and the University of Northern Colorado Cancer Rehabilitation Institute, University of Northern Colorado, USA

*Corresponding author: Reid Hayward, School of Sport and Exercise Science, University of Northern Colorado Cancer Rehabilitation Institute, University of Northern Colorado, 2780 Gunter Hall Greeley, CO 80639, USA, Tel: 970-351-1821; Fax: 970-351-1762; E-mail: reid.hayward@unco.edu

Received date: November 22, 2017; Accepted date: November 27, 2017; Published date: November 29, 2017

Copyright: © 2017 Kee Shackelford DY, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Utilizing protocols to obtain peak oxygen consumption (VO₂peak) that were designed for the apparently health population may be inappropriate for cancer survivors (CS). The University of Northern Colorado Cancer Rehabilitation Institute (UNCCRI) has developed a treadmill protocol designed for CS to address this issue.

Objective: To assess the construct validity of VO₂ peak prediction equations for the UNCCRI multistage treadmill protocol against obtained VO₂peak values in a population of CS.

Methods: Forty-five CS completed the UNCCRI VO₂peak treadmill protocol utilizing gas analysis (GAS) to obtain a true VO₂peak value. A VO₂peak value was also estimated from the gas analysis test (EstGAS) using American College of Sports Medicine's (ACSM) prediction equations. Additionally, a separate UNCCRI treadmill protocol not using gas analysis (NoGAS) was conducted using ACSM VO₂ prediction equations to determine VO₂peak. An ANOVA was used to compare GAS, EstGAS, and NoGAS to assess the validity of the prediction equations versus the VO₂peak obtained from gas analysis. A paired t-test was utilized to compare treadmill times between GAS and NoGAS to assess differences attributed to the use of gas analysis. A Pearson correlation was used to analyze the relationship between GAS and EstGAS VO₂ peak values.

Results: VO₂ peak (mL•kg⁻¹•min⁻¹) did not significantly differ between GAS (26.8±7.0), EstGAS (26.2±6.5), and NoGAS (27.1±6.5) (P=0.2). Total treadmill time (min) differed significantly between GAS (12.1±2.8) and NoGAS (12.6±3.0; P<0.05). A significant, strong positive correlation was observed in VO₂peak values between GAS and EstGAS (r=0.9; P<0.001).

Conclusion: The UNCCRI treadmill protocol accurately predicts VO₂peak when using gas analysis and when used with ACSM's prediction equations demonstrating its construct validity. The UNCCRI treadmill protocol offers a safe and alternative measure of VO₂peak for the cancer population.

Keywords: Oncology; Exercise testing; VO₂peak; Aerobic capacity; Treadmill; Cancer rehabilitation; Cancer survivor

Introduction

Physical activity performed before, during, and following cancer treatment has been shown to play an integral role in the improvement of many physiological and psychological variables, such as maximal oxygen consumption (VO₂max) and quality of life (QOL) [1,2]. VO₂ max, obtained *via* a metabolic cart utilizing gas analysis, is considered to be the best indicator of aerobic capacity [3,4]. Greater VO₂max values have been associated with reduced all-cause cancer mortality [5,6], while lower VO₂max values are among the strongest predictors of the risk of death [5,7,8]. This highlights the importance of establishing accurate VO₂max values when designing rehabilitative exercise interventions. Although VO₂max is considered to be the best measure of aerobic capacity, peak oxygen consumption (VO₂peak) may be used in its place due to the difficulties in achieving all

necessary VO₂max criteria [9]. In clinical settings, VO₂peak values have been shown to yield equivalently accurate values as VO₂max when assessing aerobic capacity [10-13] and may be more feasible to attain in cancer survivors (CS).

Exercise testing has become an important resource for obtaining VO₂peak in clinical rehabilitation [14], allowing clinicians to form accurate exercise prescriptions and guide the dosage of exercise. Treadmill running/walking and cycle ergometer protocols are the most commonly used modalities for VO₂peak testing [15], with treadmill protocols consistently eliciting higher and more accurate VO₂peak values than cycle ergometer protocols [16-18]. Most of these protocols utilize validated prediction equations to indirectly calculate VO₂peak when a metabolic cart is unavailable to obtain direct VO₂peak values. To date, one common method to indirectly estimate VO₂peak from treadmill protocols is to utilize the American College of Sports Medicine (ACSM) walking and running VO₂ equations. The Bruce treadmill protocol, which is used by more than half of the clinicians in

North America [19,20], is highly correlated with VO₂peak and is considered to be one of the most accurate protocols in measuring aerobic capacity. However, protocols like the Bruce that has large and abrupt single-stage increases in speed and grade may be unsuitable and unsafe for CS due to cancer-specific side effects. Treatment-related toxicities include musculoskeletal impairments, cardiovascular dysfunction, cachexia, gait disparities, balance issues, peripheral neuropathy, and cancer-related fatigue. These side effects may lead to early test termination in CS using treadmill protocols designed for populations other than cancer, and may not yield accurate measurements of VO₂peak [21-23].

Modified and less intense protocols have been created and validated for the apparently healthy population, such as the modified Bruce, Balke-Ware, and the United States Air Force Space and AeroMedicine (USAFSAM) protocols [24-26]. However, none of these protocols have been validated for cancer survivors. There has yet to be a protocol developed specifically for the cancer population that accounts for cancer side effects and cancer treatment toxicities. To address this issue, the University of Northern Colorado Cancer Rehabilitation Institute (UNCCRI) developed a multi-stage treadmill protocol for the measurement of VO₂peak in the cancer population. This protocol was designed to increase speed and grade in minimal increments with shorter stages, providing a more gradual increase in intensity, accounting for the numerous toxicities experienced by this population. Unlike the sudden, large increases in intensity of the Bruce protocol [27,28], the slowed progression of intensity with the UNCCRI protocol may be perceived as less intimidating for CS. The lower intensities associated with the UNCCRI protocol may allow CS to exercise longer, thereby increasing the likelihood of obtaining a true VO₂peak value and allow clinicians the ability to accurately prescribe exercise.

Exercise-based cancer rehabilitation programs are serving an integral role in assisting CS in their recovery process. Establishing an accurate VO₂peak value is one of the first and foremost steps in this process, because optimal exercise intensity cannot be prescribed without an accurate assessment of functional capacity. Additionally, due to the expensive nature of gas analysis equipment, or the lack of trained personnel, treadmill protocols should be validated with standardized VO₂peak prediction equations so that a true VO₂peak value can be obtained, regardless of equipment. Thus, there is a clear need to examine the validity of the cancer-specific UNCCRI protocol. Therefore, the purpose of this study was to assess the construct validity of the UNCCRI multi-stage treadmill protocol using VO₂peak prediction equations with a true VO₂peak obtained by gas analysis using a metabolic cart. It was hypothesized that VO₂peak obtained from the UNCCRI protocol using gas analysis (GAS) would not differ from VO₂peak estimated from the last completed stage of GAS (EstGAS) using ACSM's walking and running VO₂peak prediction equations for CS. Additionally, it was hypothesized that VO₂peak values would differ between GAS and NoGAS.

Methods

Participant cohort, setting, and procedures

Participants (n=45) were recruited from walk-in and oncologist-referred patients at UNCCRI. Prior to any study procedures, a detailed medical history was completed and informed consent obtained. All study procedures were reviewed and approved by the University of Northern Colorado Institutional Review Board. All major cancer types were represented: breast, prostate, colorectal, lung, leukemia,

lymphoma, skin, uterine, multiple myeloma, and thyroid. Participants were excluded if they had a history of congestive heart failure, myocardial infarction, asthma, significant ambulatory issues, coughing up blood, fainting, and/or epilepsy. Participants completed the UNCCRI Protocol two times: 1) with gas analysis (GAS) and 2) without gas analysis (NoGAS), yielding direct and indirect measurements of VO₂peak, respectively. Indirect estimation was conducted using ACSM's walking and running prediction equations, depending upon whether the subject was walking or running during the final stage of the test. Additionally, VO₂peak was indirectly estimated from the gas analysis protocol (EstGAS) using the ACSM's prediction equations from the GAS protocol. The protocols were completed one week apart and the order was randomized for each subject. Following testing, GAS VO₂peak values were compared with the EstGAS VO₂peak values to determine the validity in using ACSM's prediction equations with the UNCCRI protocol. Additionally, GAS values were compared to NoGAS values to observe differences in VO₂peak or treadmill times between conditions. Following testing, direct VO₂peak values (GAS) were compared with the estimated VO₂peak values (EstGAS) to determine the validity in using ACSM's prediction equations with the UNCCRI protocol. Additionally, GAS values were compared to NoGAS values to determine whether the use of a metabolic cart affected VO₂peak or treadmill times.

Pre-Test measurements and instructions

The UNCCRI protocol consisted of 21-one-minute-stages. Speed and/or grade were increased at the completion of each stage (Table 1). If any participant was able to complete stage 20, the speed was increased by 0.1 mile per hour (mph) and grade by 1% every minute until fatigue was elicited. Resting blood pressure (BP), heart rate (HR), blood oxygen saturation (SpO₂), and body weight were measured before all tests. Blood pressure was determined using manual auscultation *via* a sphygmomanometer and stethoscope, HR was determined using a Polar® heart rate monitor, and SpO₂ was determined using a Clinical Guard® pulse oximeter. During all tests SpO₂ and HR were recorded every minute and rating of perceived exertion (RPE) and BP were recorded every three minutes. Four clinicians were utilized during each protocol and were responsible for changing the speed and grade of the treadmill and recording vitals, taking blood pressure, spotting the subject from behind, and operating the metabolic cart.

Stage	Speed	Grade	Time
0	1.0 mph	0%	1 min
1	1.5 mph	0%	1 min
2	2.0 mph	0%	1 min
3	2.5 mph	0%	1 min
4	2.5 mph	2%	1 min
5	3.0 mph	2%	1 min
6	3.3 mph	3%	1 min
7	3.4 mph	4%	1 min
8	3.5 mph	5%	1 min
9	3.6 mph	6%	1 min

10	3.7 mph	7%	1 min
11	3.8 mph	8%	1 min
12	3.9 mph	9%	1 min
13	4.0 mph	10%	1 min
14	4.1 mph	11%	1 min
15	4.2 mph	12%	1 min
16	4.3 mph	13%	1 min
17	4.4 mph	14%	1 min
18	4.5 mph	15%	1 min
19	4.6 mph	16%	1 min
20	4.7 mph	17%	1 min
Cool-Down	**	0%	**

Table 1: UNCCRI Protocol (**Denotes no standard number and is subject to change dependent on the patient).

For all tests, participants were discouraged from using the handrails for the entirety of the protocol unless it was deemed necessary due to increased risk or patient discomfort. The tests terminated when the participant reached their maximum threshold of exertion and could not continue any further. Additional test termination criteria included: HR did not increase with increased intensity, systolic blood pressure (SBP) did not increase with increased intensity, diastolic blood pressure (DBP) oscillated more than 10 mmHg from resting measure, SpO₂ dropped below 80%, and/or verbal consent of the participant to end the test due to safety issues. A cool down period was conducted after completion of the test to ensure that the participant returned to near resting vital measures. Final HR, BP, SpO₂, and treadmill time were recorded.

Before each treadmill test began, all participants were given the following instructions: 1) a clinician will be recording all data from the test, as well as changing the speed and grade of the treadmill, 2) another clinician will be taking your BP once every three minutes, 3) a pulse oximeter will be placed on your index finger, which will display your SpO₂ at the end of every minute, 4) another clinician will be standing behind the treadmill for spotting purposes, 5) we would like you to push yourself to what you feel is your maximum exertion; you may stop the test at any point, but we would like you to reach the point where you feel you cannot physically continue, 6) we recommend you do not use the handrails, but you may if you feel it is necessary, 7) regardless of whether you choose to use or not to use handrails, you must choose one for the entire duration of the test, you may not go back and forth, and 7) once you reach perceived maximal exertion, we will begin a cool-down to return your vitals to near resting values.

A test was deemed a true VO₂peak test if at least two of the following criteria were met: 1) participant terminated test due to perceived maximal effort and fatigue, 2) HR was elevated to within ten beats per minute of the individual's estimated maximal heart rate, and 3) if a participant verbalized a RPE value on the modified Borg scale of at least eight. If the criteria were not met, the test results were not used.

UNCCRI gas analysis protocol

During the GAS test, all participants completed the UNCCRI protocol exactly as described above with the addition of gas analysis. Using a 35 Series Data Acquisition System research grade metabolic cart (ADInstruments, Colorado Springs, CO), expired gases were continuously collected and VO₂ and VCO₂ were recorded once every 10 s. Calibration of the metabolic cart was performed before each test with a 3L syringe and precision gas mixtures (ADInstruments, Colorado Springs, CO). Before the test began, each participant received a detailed explanation as to how the test would be conducted, and why the metabolic cart was being used. Participants wore a face mask that was held in place by fitted straps. A tube connected the face mask to the metabolic cart. Participants were instructed to breathe primarily through their mouths, not their noses. The face mask made the participant inaudible, so participants were instructed to give RPE using their fingers. Peak oxygen consumption was determined by taking the highest VO₂ value that was observed during the test and was recorded in liters per minute (L/min). To convert this to mL•kg⁻¹•min⁻¹, the following equation was used: [(L/min × 1000)/ body weight (kg)]. In addition to standard termination criteria, this protocol ended if VO₂ reached a plateau. Upon termination, the participant began a cool-down period.

UNCCRI protocol without gas analysis (NoGAS)

ACSM walking and running equations were used to estimate VO₂peak by using the last completed stage of the GAS protocol. The participant determined whether he or she needed to walk or run during the final stages. If the participant was walking without handrail usage during the last completed stage, the following equation was used: VO₂peak=(0.1 × S)+(1.8 × S × G)+3.5; where S= speed and G=grade [29]. If a participant was holding onto the handrails and walking during the last completed stage, the following correction equation was used: VO₂peak=0.694 [(0.1 × S)+(1.8 × S × G)+3.5]+3.33 [29,30]. If the participant was running without handrail usage during the last completed stage, the following equation was used: VO₂peak=(0.2 × S) + (0.9 × S × G)+3.5 [29]. If the participant was running and holding on to the handrails during the last completed stage the following correction equation was used: VO₂peak=0.694 [(0.2 × S)+(0.9 × S × G) +3.5]+3.33 [29,30]. The computed value was then compared to the value obtained from GAS to detect effects of the metabolic cart on treadmill time or VO₂peak.

Estimated VO₂peak from gas analysis (EstGAS)

ACSM walking and running equations were used to estimate VO₂peak by using the last completed stage of the GAS protocol following the same procedures and equations from NoGAS. This value (EstGAS) was then compared to the direct value obtained *via* GAS to determine validity of the UNCCRI protocol.

Statistical analysis

Prior to the start of the study a power analysis was conducted using the statistical program G-Power (version 3.1) to determine the appropriate sample and effect sizes. Using the differences and the standard deviations between observations, a medium effect size was used for the participants with a confidence level of 95%. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL.). All data are presented as mean ± standard deviation (SD). An ANOVA was used to examine differences

in VO₂peak values between GAS, EstGAS, and NoGAS. A dependent t-test was utilized to determine differences in treadmill times between GAS and NoGAS. A Pearson-r correlation was conducted to examine the strength of relationship for VO₂peak between GAS and EstGAS. Significance levels for all tests were set at P<0.05.

Result

Participant characteristics

Of the 45 CS that participated in this study, 12 (27%) underwent surgery alone, two (4%) underwent radiation alone, six (13%)

underwent surgery and radiation treatments, one (2%) underwent radiation and chemotherapy, nine (20%) underwent surgery and chemotherapy, and 15 (34%) underwent surgery, chemotherapy, and radiation. All participants were able to achieve VO₂peak criteria, and no adverse effects were observed during or after any of the VO₂peak tests.

Heart rate and blood pressure responses

Heart rate significantly increased from baseline to peak exercise for GAS (83 ± 13 to 159 ± 8; P<0.001) as well as NoGAS (83 ± 13 to 157 ± 19; P< 0.001).

	GAS	EstGAS	NoGAS	P-Value
HR	159 ± 17	-	157 ± 19	0.6
SBP	150 ± 14	-	152 ± 13	0.31
DBP	76 ± 19	-	79 ± 8	0.76
RPE	9.0 ± 1.0	-	9.0 ± 1.0	0.2
RER	0.9 ± 0.1	-	-	-
Treadmill time (min)	12.1 ± 2.8	-	12.6 ± 3.0	<0.05*
VO ₂ (mL•kg ⁻¹ •min ⁻¹)	26.8 ± 7.0	26.2 ± 6.5	27.1 ± 6.5	0.80
VO ₂ (L/min)	1.9 ± 0.4	1.9 ± 0.8	2.0 ± 0.8	0.82
VO ₂ (METS)	7.6 ± 2.0	7.4 ± 2.2	7.7 ± 1.8	0.81

Table 2: Mean Peak Exercise Values (GAS: University of Northern Colorado Cancer Rehabilitation Institute gas analysis protocol; EstGAS: University of Northern Colorado Cancer Rehabilitation Institute estimated peak volume of oxygen consumption from gas analysis protocol; NoGAS: University of Northern Colorado Cancer Rehabilitation Institute no gas analysis protocol; VO₂: Volume of Oxygen Consumption; HR: Heart Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; RPE: Rating of Perceived Exertion; RER: Respiratory Exchange Ratio; *denotes P value<0.05 between GAS vs. NoGAS;-signifies same obtained value from GAS).

Systolic blood pressure also significantly increased from rest to peak performance during GAS (121 ± 13 to 150 ± 14; P<0.001) and NoGAS (123 ± 13 to 152 ± 13; P <0.001), and did not differ between GAS and NoGAS. Diastolic blood pressure did not change significantly from resting measures during any treadmill testing (P>0.05) (Table 2).

Validity of VO₂peak protocol for cancer survivors

Table 2 depicts average peak treadmill variables, and compares VO₂peak values between GAS, EstGAS, and NoGAS. The mean relative VO₂peak (mL•kg⁻¹•min⁻¹) did not significantly differ between GAS (26.8 ± 7.0), EstGAS (26.2 ± 6.5), or NoGAS (27.1 ± 6.5) (P=0.8). Significant differences in treadmill times were observed between GAS and NoGAS (12.1 ± 2.8 vs. 12.6 ± 3.0) (P<0.05). Significant positive VO₂peak correlations were observed between GAS and EstGAS (r=0.90; P<0.001) (Figure 1).

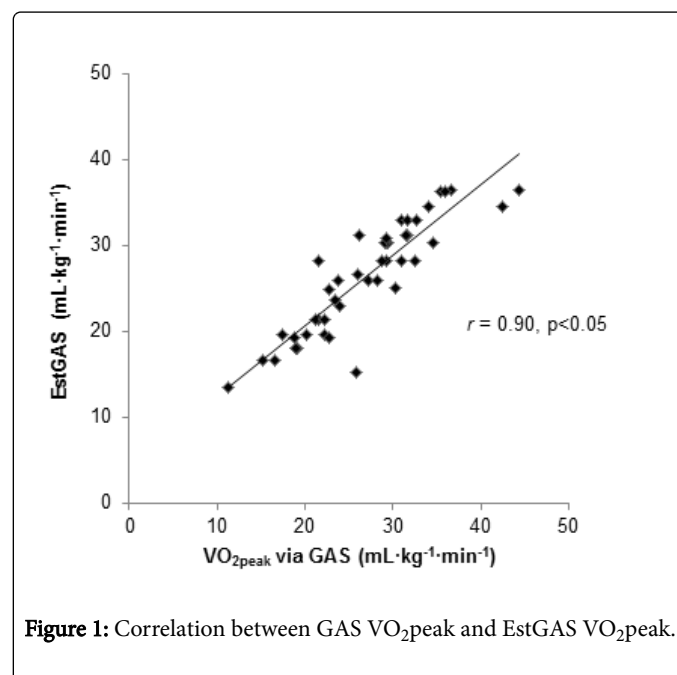


Figure 1: Correlation between GAS VO₂peak and EstGAS VO₂peak.

Discussion

The primary purpose of this study was to assess the validity of the UNCCRI multi-stage treadmill protocol's VO₂peak prediction equations for a cancer-specific population with standard metabolic gas analysis. The principal finding was that VO₂peak obtained from direct gas analysis did not significantly differ from the indirect estimation of VO₂peak using ACSM metabolic equations. Additionally, VO₂peak values for GAS and EstGAS were highly and significantly correlated ($r=0.91$, $P<0.05$). All tests met VO₂peak criteria and the ACSM equations accurately estimated VO₂peak when used with the UNCCRI treadmill protocol in cancer survivors. Similar correlations have been reported between directly measured and predicted VO₂peak values for established VO₂peak protocols such as the modified Balke and the modified Naughton tests [26,31-33]. Ramp protocols such as the UNCCRI protocol demonstrate a positive linear relationship between oxygen uptake and work rate [34], which supports the non-significant differences between measured and estimated VO₂peak from the GAS test. Similar studies observed a strong correlation ($r=0.92$) between ACSM's prediction equations and VO₂ [27]. It has also been reported that correlations between the Bruce protocol's predicted VO₂max and directly measured VO₂max was 0.94 in apparently healthy populations [35]. These findings support our hypothesis and indicate that using ACSM's walking and running equations is a valid method for determining VO₂peak using the UNCCRI protocol.

The secondary principle finding was that indirect estimation of peak oxygen consumption did not differ between the GAS and NoGAS protocols. This supports the notion that the UNCCRI protocol can accurately estimate VO₂peak without the use of a metabolic cart. However, total treadmill time of the NoGAS (12.7 ± 3.0 min) was significantly higher than treadmill time from the GAS (12.1 ± 2.8 min; $P<0.05$). To our knowledge, this is the first study to address whether the metabolic cart, or more specifically the gas analysis face mask, might hinder treadmill performance in CS. The shorter treadmill time on GAS may be explained entirely by the use of the face mask. Multiple participants reported it to cause claustrophobia, breathing difficulties, shortness of breath, throat irritation, dry mouth, and feelings of discomfort. The difficulties experienced by our participants due to obstruction of normal breathing is not unfounded [36,37]. Participants disliked how the face mask and tubing restricted any movement of the head, and stated that not being able to look in any other direction but forward affected their balance and stability, fearing the increased risk of tripping or falling. Balance deficiencies (e.g., vertigo, ataxia, peripheral neuropathy) are a common side effect of cancer treatments [38,39] and may be especially problematic for CS who are required to wear equipment that might further exacerbate these side effects. Cancer survivors suffering from treatment-related balance loss reported greater difficulties during the direct gas analysis protocol since they were unable to look down to concentrate on foot placement. Complications experienced with the gas analysis face mask may explain why GAS treadmill times were significantly less than NoGAS. This further supports the notion that while gas analysis may be the most accurate method of determining VO₂peak, the equipment involved with this specialized testing may actually negatively affect treadmill testing time in CS.

The UNCCRI protocol does not tax the lower body as vigorously as other established treadmill tests. Protocols that utilize steeper inclines, such as the Bruce protocol, will lead to a greater reliance on anaerobic metabolism, causing participants to reach fatigue more quickly [40-42]. Cancer survivors may be experiencing cancer cachexia and/or

detrimental treatment-related muscular toxicities which may adversely affect ATP stores and result in severe fatigue with or without physical exertion [38,43]. As a result, many CS may terminate other treadmill protocols earlier due to factors outside cardiovascular function, such as fatigue and/or muscular endurance. This response is not necessarily exclusive to CS. Other studies have reported difficulties achieving target heart rate during the Bruce protocol in a general patient population due to the physical inability to maintain the large incremental changes in workload [28]. Because the UNCCRI protocol is designed to be more tolerable for CS, reduced stress is placed on the musculoskeletal system, decreasing the risk of early test termination from muscular fatigue.

Other modified and less strenuous protocols have been developed, such as the modified Bruce and the Balke-Ware protocols. However, these protocols are not cancer population specific and were not developed with the treatment-related toxicities associated with cancer and its treatments in mind. The modified Bruce implements increases in grade as large as 5% between stages and utilizes stages that are 3 minutes in duration. The Balke-Ware protocol incorporates rapid increases in grade from the outset of the test and quickly reaches greater inclines that can lead to early-onset fatigue. These protocols may be unsuitable for certain groups, such as the gerontological population, due to the risk of injury and difficulty completing the early stages of the test [8,44,45]. Additionally, the median age of cancer diagnosis is 65 years of age, and other validated protocols have been deemed unsuitable for the gerontological population due to general exhaustion [46]. Because CS experience unique detrimental side effects, a protocol should be designed with cancer specific side-effects in mind, just as the modified Naughton protocol was tailored for individuals diagnosed with congestive heart failure [25].

Treadmill tests were created to specifically assess the cardiovascular system, and researchers and clinicians must ensure that weaknesses in other physiological systems, such as the musculoskeletal system, do not confound results. The UNCCRI treadmill protocol was designed to implement stages that are more gradual and attainable compared to other treadmill protocols. There are no drastic increases in incline like the Bruce or modified Bruce protocol, and no constant speeds that may be too fast for CS, as observed in the Balke protocol. Instead, CS is able to start off at a very low intensity and gradually work their way to a higher intensity. The smaller grades and slower speeds during the early stages of the protocol accommodate musculoskeletal, pulmonary, and cardiovascular side effects caused by standard cancer treatments. The goal of the UNCCRI protocol is to have CS reach VO₂ values close to maximal without early termination. The first stage and progression of the UNCCRI protocol is manageable for CS with the most severe toxicities, starting at a speed of 1.0 mph at a 0% incline. This protocol utilizes a mode of progression that does not rely on maximal work rate until the later stages. With the exception of the first initial increase in incline (+2%), the incline is never increased by more than 1% per minute and speed is increased by 0.1 mph per minute for the majority of the test. The shorter stages allow CS to complete entire stages more often, which allows clinicians to more accurately calculate VO₂peak.

Exercise-based programs are becoming more widely utilized in comprehensive cancer rehabilitation programs. It is critical that valid, standardized tests exist to provide the most accurate measures of physical function in CS. Currently there is no standardized VO₂peak test that has been developed for the CS population. The present study examined the validity of the first treadmill VO₂peak assessment for the cancer population, the UNCCRI multi-stage treadmill protocol. Peak

oxygen consumption from GAS did not significantly differ from EstGAS nor NoGAS, suggesting that ACSM's walking and running equations are a valid method of estimating VO₂peak from the UNCCRI protocol. The UNCCRI protocol was specifically designed to decrease the magnitude of intensity change experienced with each stage, allowing CS suffering from cancer side-effects and treatment-related toxicities to progress further into the protocol, resulting in a more precise VO₂peak value. Our clinic has been conducting aerobic capacity assessments utilizing the UNCCRI treadmill protocol for over six years. During this time no adverse events or effects have been observed, and this protocol has consistently yielded VO₂peak values that are integral for the development of an accurate exercise prescription. The UNCCRI treadmill protocol is a valid measure of VO₂peak for CS, and offers a safe and effective test for the CS population.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Acknowledgments

The authors thank all members of UNCCRI who assisted with data collection. We would also like to recognize Dr. Carole Schneider, the founder and creator of UNCCRI.

Conflict of Interest

The authors declare no conflicts of interest.

References

1. Anderson RT, Kimmick GG, McCoy TP, Hopkins J, Levine E, et al. (2012) A randomized trial of exercise on well being and function following breast cancer surgery: The RESTORE trial. *J Cancer Surviv* 6: 172-181.
2. Groeneveldt L, Mein G, Garrod R, Jewell AP, Van Someren K, et al. (2013) A mixed exercise training programme is feasible and safe and may improve quality of life and muscle strength in multiple myeloma survivors. *BMC Cancer* 13: 31.
3. Scott JM, Hornsby WE, Lane A, Kenjale AA, Eves ND, et al. (2015) Reliability of maximal cardiopulmonary exercise testing in men with prostate cancer. *Med Sci Sports Exerc* 47: 27-32.
4. Wall BA, Galvao DA, Fatehee N, Taaffe DR, Spry N, et al. (2014) Maximal exercise testing of men with prostate cancer being treated with androgen deprivation therapy. *Med Sci Sports Exerc* 46: 2210-2215.
5. Myers J, Prakash M, Froelicher V, Do D, Partington S, et al. (2002) Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 346: 793-801.
6. Sawada SS, Muto T, Tanaka H, Lee IM, Paffenbarger RS, et al. (2003) Cardiorespiratory fitness and cancer mortality in Japanese men: A prospective study. *Med Sci Sports Exerc* 35: 1546-1550.
7. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, et al. (2010) ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 56: e103-e109.
8. Stone C, Lawlor PG, Nolan B, Kenny RA (2011) A prospective study of the incidence of falls in patients with advanced cancer. *J Pain Symptom Manage* 42: 535-540.
9. Midgley AW, McNaughton LR, Polman R, Marchant D (2007) Criteria for determination of maximal oxygen uptake. *Sports Medicine* 37: 1019-1028.
10. Day JR, Rossiter HB, Coats EM, Skasick A, Whipp BJ (2003) The maximally attainable VO₂ during exercise in humans: The peak vs. maximum issue. *J Appl Physiol* 95: 1901-1907.
11. Howley ET (2007) VO₂max and the plateau--needed or not? *Med Sci Sports Exerc* 39: 101-102.
12. Jones LW, Liang Y, Pituskin EN, Battaglini CL, Scott JM, et al. (2011) Effect of exercise training on peak oxygen consumption in patients with cancer: A meta-analysis. *Oncologist* 16: 112-120.
13. Kim CJ, Kang DH, Smith BA, Landers KA (2006) Cardiopulmonary responses and adherence to exercise in women newly diagnosed with breast cancer undergoing adjuvant therapy. *Cancer Nurs* 29: 156-165.
14. American Thoracic Society, American College of Chest Physicians (2003) ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 167: 211-277.
15. De Lucas RD, Rocha R, Burini R, Greco CC, Denadai B (2003) The lactate minimum test protocol provides valid measures of cycle ergometer VO₂peak. *J Sports Med Phys Fitness* 43: 279.
16. Dabney U, Butler M (2006) Predictive ability of the YMCA test and bruce test for triathletes with different training backgrounds. *Emporia State Research Studies* 43: 38-44.
17. Moody DL, Kollias J, Buskirk ER (1969) Evaluation of aerobic capacity in lean and obese women with four test procedures. *J Sports Med Phys Fitness* 9: 1-9.
18. Pollock ML, Foster C, Schmidt D, Hellman C, Linnerud A, et al. (1982) Comparative analysis of physiologic responses to three different maximal graded exercise test protocols in healthy women. *Am Heart J* 103: 363-373.
19. Chugh S (2006) Textbook of clinical electrocardiography. 3rd ed. Jaypee Brothers, Medical Publishers.
20. Marinov B, Kostianev S, Turnovska T (2003) Modified treadmill protocol for evaluation of physical fitness in pediatric age group-comparison with bruce and balke protocols. *Acta Physiol Pharmacol Bulg* 27: 47-51.
21. Cunha FA, Catalao RP, Midgley AW, Gurgel J, Porto F, et al. (2012) Do the speeds defined by the American College of Sports Medicine metabolic equation for running produce target energy expenditures during isocaloric exercise bouts? *Eur J Appl Physiol* 112: 3019-3026.
22. Foster C, Jackson AS, Pollock ML, Taylor MM, Hare J, et al. (1984) Generalized equations for predicting functional capacity from treadmill performance. *Am Heart J* 107: 1229-1234.
23. Lee JM, Bassett DR, Thompson DL, Fitzhugh EC (2011) Validation of the cosmed fitmate for prediction of maximal oxygen consumption. *J Strength Cond Res* 25: 2573-2579.
24. Balke B, Ware RW (1959) An experimental study of physical fitness of air force personnel. *U S Armed Forces Med J* 10: 675-688.
25. Patterson JA, Naughton J, Pietras RJ, Gunnar RM (1972) Treadmill exercise in assessment of the functional capacity of patients with cardiac disease. *Am J Cardiol* 30: 757-762.
26. Wolthuis RA, Froelicher VF, Fischer J, Noguera I, Davis G, et al. (1977) New practical treadmill protocol for clinical use. *Am J Cardiol* 39: 697-700.
27. Bader DS, Maguire TE, Balady GJ (1999) Comparison of ramp versus step protocols for exercise testing in patients ≥ 60 years of age. *Am J Cardiol* 83: 11-14.
28. Will PM, Walter JD (1999) Exercise testing: Improving performance with a ramped bruce protocol. *Am Heart J* 138: 1033-1037.
29. American College of Sports Medicine (2013) ACSM's guidelines for exercise testing and prescription. Lippincott Williams & Wilkins.
30. Foster C, Schaller K, Greany J, Gibson MH, Porcari JP (2007) Accuracy of the ACSM equation for predicting VO₂ during treadmill walking. *J Cardiopulmonary Rehab Prev* 27: 329.
31. Ebbeling CB, Ward A, Puleo EM, Widrick J, Rippe JM (1991) Development of a single-stage submaximal treadmill walking test. *Med Sci Sports Exerc* 23: 966-973.

32. Martin D, Acker Jr JE (1988) Predicting aerobic capacity during the modified naughton treadmill protocol in patients with coronary artery disease. *J Cardiopulmonary Rehab Preven* 8: 297-302.
33. Singh SJ, Morgan MD, Hardman AE, Rowe C, Bardsley PA (1994) Comparison of oxygen uptake during a conventional treadmill test and the shuttle walking test in chronic airflow limitation. *Eur Respir J* 7: 2016-2020.
34. Myers J, Buchanan N, Smith D, Neutel J, Bowes E, et al. (1992) Individualized ramp treadmill: Observations on a new protocol. *Chest* 101: 236S-41S.
35. Bruce R, Kusumi F, Hosmer D (1973) Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J* 85: 546-562.
36. Gardiner DM, Ranalli DN (2000) Attitudinal factors influencing mouthguard utilization. *Dent Clin North Am* 44: 53-65.
37. Yarar H, Karli U, Aydin K, Erdem H, Uzum H (2013) Effect of using mouth guard on anaerobic and aerobic performance of combat sport athletes. *Age* 22: 2.
38. Schneider C, Hayward R (2013) Cancer rehabilitation and cancer-related fatigue. *J Clinical Exercise Physiol* 2: 1-7.
39. Bart BA, Wolfel EE (1994) Method of expired gas collection during cardiopulmonary exercise testing does not affect respiratory gas exchange measurements in patients with heart failure. *J Card Fail* 1: 91-96.
40. Bottinelli R, Reggiani C (2000) Human skeletal muscle fibres: Molecular and functional diversity. *Prog Biophys Mol Biol* 73: 195-262.
41. Boyas S, Guével A (2011) Neuromuscular fatigue in healthy muscle: Underlying factors and adaptation mechanisms. *Ann Phys Rehabil Med* 54: 88-108.
42. Westerblad H, Bruton JD, Katz A (2010) Skeletal muscle: Energy metabolism, fiber types, fatigue and adaptability. *Exp Cell Res* 316: 3093-3099.
43. Berger AM, Gerber LH, Mayer DK (2012) Cancerrelated fatigue. *Cancer* 118: 2261-2269.
44. Wampler MA, Topp KS, Miaskowski C, Byl NN, Rugo HS, et al. (2007) Quantitative and clinical description of postural instability in women with breast cancer treated with taxane chemotherapy. *Arch Phys Med Rehabil* 88: 1002-1008.
45. Winters-Stone KM, Torgrimson B, Horak F, Eisner A, Nail L, et al. (2011) Identifying factors associated with falls in postmenopausal breast cancer survivors: A multi-disciplinary approach. *Arch Phys Med Rehabil* 92: 646-652.
46. Aguiar J, Reis R, Caria R, Nunes H, de Almeida A, et al. (1997) Stress tests in old age. the choice of the stress protocol. *Acta Médica Portuguesa* 10: 311-316.