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UNIVERSITY OF NORTHERN COLORADO

Greeley, Colorado

The Graduate School

VALIDATION OF THE ROCKY MOUNTAIN CANCER REHABILITATION  
INSTITUTE MULTISTAGE TREADMILL PROTOCOL  
FOR CANCER SURVIVORS

A Dissertation Submitted in Partial Fulfillment  
of the Requirements for the Degree of  
Doctor of Philosophy

Daniel Yoon Kee Shackelford

College of Natural and Health Sciences  
School of Sport and Exercise Science  
Exercise Physiology

May 2015

This Dissertation by: Daniel Yoon Kee Shackelford

Entitled: *Validation of the Rocky Mountain Cancer Rehabilitation Institute Multistage Treadmill Protocol for Cancer Survivors*

has been approved as meeting the requirements for the Degree of Doctor of Philosophy in the College of Natural and Health Sciences in The School of Sport and Exercise Science, Program of Exercise Science

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## ABSTRACT

Shackelford, Daniel Yoon Kee. *Validation of the Rocky Mountain Cancer Rehabilitation Institute Multistage Treadmill Protocol for Cancer Survivors*. Published Doctoral Dissertation, University of Northern Colorado, 2015.

Many exercise testing protocols used in clinical settings have been developed for apparently healthy (AH) populations, but may be inappropriate for cancer survivors (CS) due to cancer and treatment-related toxicities. The Rocky Mountain Cancer Rehabilitation Institute (RMCRI) developed a cancer specific treadmill protocol to specifically address this issue. **Purpose:** To assess the validity of the RMCRI multistage treadmill protocol. **Methods:** 61 participants (45 CS, 16 AH controls) completed three different treadmill protocols, the Bruce (BTP) (for AH subjects), RMCRI without gas analysis (RWO GAP), and RMCRI with gas analysis (RGAP), to compare values of peak oxygen consumption ( $VO_{2peak}$ ). Participants completed the trials one week apart in random order. Obtained  $VO_{2peak}$  values from RGAP were compared against estimated  $VO_{2peak}$  from the same gas analysis (GA) test using the American College of Sports Medicine (ACSM) prediction equations (EVACSM).  $VO_{2peak}$  from RGAP was also compared to the estimated values of  $VO_{2peak}$  achieved during the Bruce protocol. Finally,  $VO_{2peak}$  from RGAP was compared against predicted  $VO_{2peak}$  values obtained from RWO GAP. Correlations were run between all protocols for each group. **Results:** For AH participants, no significant differences were observed between any of the

VO<sub>2</sub>peak protocol values ( $p > 0.05$ ), and positive strong correlations occurred between all protocols ( $r > 0.8$ ). Among CS, VO<sub>2</sub>peak between RGAP and BTP were significantly different ( $p < 0.05$ ). No significant differences in VO<sub>2</sub>peak values occurred between RGAP and EVACSM ( $p > 0.05$ ). A positive strong correlation occurred between RGAP VO<sub>2</sub>peak and EVACSM ( $r = 0.90$ ), and between VO<sub>2</sub>peak from the RGAP and RWO GAP ( $r = 0.81$ ). A moderate positive correlation was observed between VO<sub>2</sub>peak values from BTP and RGAP ( $r = 0.51$ ). CS group treadmill time was significantly greater on RWO GAP ( $12.6 \pm 2.8$  min) than RGAP ( $12.1 \pm 2.8$  min) ( $p < 0.05$ ).

**Conclusion:** Our findings suggest that the Bruce protocol is not an appropriate protocol for CS. GA equipment may also negatively affect treadmill performance as well. The observed high correlations and validity between predicted and observed VO<sub>2</sub>peak values suggest that the RMCRI cancer-specific protocol is a valid method of determining VO<sub>2</sub>peak and should be considered as the standard VO<sub>2</sub>peak treadmill test for cancer survivors.

DEDICATED TO:

DR. CAROLE M. SCHNEIDER

*No words can truly describe the impact you've had on my life. Before I knew you, I was a ship without a sail. You gave my career a direction and a dream to strive for. You were willing to take a chance on me when it seemed nobody else would. Your feisty attitude and your expectation of excellence helped mold who I am today. It was truly an honor learning from you and working alongside you. Not only did I have the privilege of having you as my mentor and my advisor, but also to the extent of an academic mother. You truly cared for me, and it showed everyday by pushing me to be the best I could be, and picking me back up when I stumbled. I experienced true compassion and genuine care from you not only as a student, but as an individual. Your strength, passion, determination, and perseverance shines as a beacon to follow. Your inspiration lives on through every single student and cancer survivor you've helped, and I promise to carry your legacy with me wherever I go. Thank you, from the bottom of my heart, for everything you've helped me achieve, and for believing I could be more than I ever dreamt possible.*

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## **CHAPTER I**

### **INTRODUCTION**

Cancer can be characterized as a group of diseases exemplified by atypical cellular growth and development. Currently, there are approximately 13.7 million Americans living with a history of cancer, and about 1,658,370 new cases of cancer are expected to be diagnosed in 2015 (American Cancer Society [ACS], 2015). Males have a greater risk of developing cancer, with slightly less than a 50% chance of being diagnosed; whereas females have a little more than a 33% chance of being diagnosed their lifetime (ACS, 2015). Unfortunately, more than a half million Americans are expected to succumb to cancer this year. Encouragingly, there are about 12 million cancer survivors (CS) in the United States and this number continues to grow every year (Schmitz et al., 2010). The 5-year survival rate for cancers diagnosed between 2002 and 2008 is now 68%, which has increased from the 49% survival rate observed between 1975-1977 (ACS, 2015). This may be a result of earlier detection and the advancement in cancer treatments.

Throughout the literature, it has been demonstrated among CS that physical activity performed before, during, and after treatment has been a substantial factor in the reported improvements in physiological and psychological factors such as increased muscular strength and endurance, increased maximal oxygen consumption ( $VO_{2max}$ ),

increased flexibility, decreased fatigue, decreased depression, and increased quality of life (QOL) (Anderson et al., 2010; Groeneveldt et al., 2013; Jones, Eves, Haykowsky, Freeland, & Mackey, 2009; Schneider, Hsieh, Sprod, Carter, & Hayward, 2007a; Schneider, Hsieh, Sprod, Carter, & Hayward, 2007b). Despite the observed positive benefits of exercise, only a small percentage of CS choose to exercise during their treatment (Murnane, Geary, & Milne, 2012). Since the benefits of exercise on cancer recovery have become better understood, a greater number of CS are requesting information about rehabilitation services (Thorsen et al., 2011). Cancer rehabilitation programs should aim to improve a cancer survivor's functional ability as well as optimize psychological well-being through formal exercise programming. Cardiovascular function is considered to be an excellent measure of overall physical fitness, and has been shown to decrease in CS as a result of cancer and cancer treatments (Doyle, Neugut, Jacobson, Grann, & Hershman, 2005; Smoot, Johnson, Duda, Krasnoff, & Dodd, 2012; Taylor et al. 2010). This decline in cardiovascular fitness may be attributed directly to treatments such as chemotherapy and radiation or may be the result of a decline in overall physical activity due to general deconditioning (Jones et al., 2009; Schneider et al., 2007b; Shapiro & Recht, 2001). Exercise has been shown to increase cardiovascular fitness and predicted  $VO_{2max}$  in a cancer population (Schneider et al., 2007b), and several studies have demonstrated that physical activity is a safe intervention for CS (Doyle et al., 2006; Nelson et al., 2007).

A  $VO_{2max}$  test using gas analysis (GA) is considered to be the gold standard for cardiorespiratory fitness, but it requires experienced personnel, expensive equipment, and compliance from patients willing to reach maximum exercise capacity (Brooks, Fahey, &

Baldwin, 2005; Kim, Kang, Smith, & Landers, 2006; Jones et al., 2011). However, protocols for this type of test are generally aimed at apparently healthy (AH) populations. For example, CS in particular may not be able to push themselves to the point of exhaustion due to the high intensities and requirements of the test. Many facilities do not have access to the equipment and personnel necessary for a true  $\text{VO}_{2\text{max}}$  test; in these instances, a  $\text{VO}_{2\text{peak}}$  test may be used, which is defined as the highest level of oxygen consumption achieved during a graded treadmill test, regardless of whether maximum criteria are met (Heyward & Gibson, 2014; Jones et al., 2007; Kim et al., 2006). These tests are generally shorter in duration than  $\text{VO}_{2\text{max}}$  tests, require no special equipment, are less stressful, and predict a value that is nearly identical to  $\text{VO}_{2\text{max}}$  (De Backer et al., 2007). In light of this information, a specifically tailored  $\text{VO}_{2\text{peak}}$  treadmill protocol is greatly needed for special populations, such as CS, to garner reliable  $\text{VO}_{2\text{peak}}$  values.

The Rocky Mountain Cancer Rehabilitation Institute (RMCRI) multi-stage treadmill protocol has been used to assess cardiovascular function in CS (Shackelford, Brown, Lalonde, Hydock, & Schneider, 2012). Intensities and grades advance during this protocol at a more manageable and appropriate pace when compared to protocols designed for AH populations. While this protocol theoretically allows clinicians to get a more accurate measure of  $\text{VO}_{2\text{peak}}$  due to a greater tolerance by CS, this protocol has not yet been fully validated. Therefore, the purpose of this study is to investigate whether the RMCRI treadmill protocol is a valid method for the measurement of  $\text{VO}_{2\text{peak}}$  in CS.

### **Statement of Purpose**

The purpose of this study was to assess the validity of the RMCRI multi-stage treadmill protocol for a cancer-specific population against standard metabolic GA and the Bruce treadmill protocol.

### **Research Hypotheses**

H1: Peak volume of oxygen consumption obtained from the RMCRI protocol using GA will not significantly differ from  $VO_{2peak}$  calculated from the last completed stage of the GA test using the American College of Sports Medicine's (ACSM) walking/running equations for either the CS or AH group.

H2: Peak volume of oxygen consumption achieved from the Bruce protocol will be significantly lower from  $VO_{2peak}$  obtained using the RMCRI protocol using GA for the CS. No significant differences will occur in the AH group.

H3: Peak volume of oxygen consumption values obtained from the RMCRI protocol using GA will not be significantly different than  $VO_{2peak}$  values obtained from a separate RMCRI protocol not using GA for either CS or AH group. This will indicate that a respiration mask used during GA does not inhibit a participant's performance on a treadmill.

### **Significance of Study**

Cardiovascular fitness is one of the best ways of determining an individual's overall health (Brooks et al., 2005; Jones, Haykowsky, Joy, & Douglas, 2008). Maximal aerobic capacity ( $VO_{2max}$ ) is the maximum amount of oxygen consumed during maximal work. This value is the best objective measure of cardiovascular fitness and provides guidance in the prescription of exercise for patients (Hawkins, Raven, Snell, Stray-

Gundersen, & Levine, 2006; Kim et al., 2006; Lakoski, Eves, Douglas, & Jones, 2012).

To achieve a true  $\text{VO}_{2\text{max}}$ , a metabolic cart and additional equipment are needed to ensure the participant reaches maximum value criterion (respiratory exchange ratio  $>1.15$ , a plateau in  $\text{VO}_2$  with an increase in exercise intensity, blood lactate exceeding  $8 \text{ mmol}\cdot\text{L}^{-1}$ , and failure to increase heart rate with an increased intensity) (Hawkins et al., 2006; Heyward & Gibson, 2014). However, metabolic carts are very expensive to obtain and require trained personnel to accurately conduct the testing. Another disadvantage of a  $\text{VO}_{2\text{max}}$  test using a metabolic cart is that it may be extremely uncomfortable for a client to perform due to the use of a face mask to measure respiration. This often leads to distress in patients who have respiratory difficulties, are claustrophobic, or who are unable to continuously breathe through their mouths.

Due to these disadvantages,  $\text{VO}_{2\text{max}}$  tests are not always a viable option. This becomes particularly true for CS who are suffering from cancer and cancer-related toxicities.  $\text{VO}_{2\text{peak}}$  tests without a metabolic cart are often used in place of  $\text{VO}_{2\text{max}}$  tests, in which the highest value of  $\text{VO}_2$  achieved during a test is recorded, regardless of whether maximum criterion are met (Jones et al., 2011; Kim et al., 2006; Maeder et al., 2010; Pina & Karalis, 1990). It should be noted that most  $\text{VO}_{2\text{peak}}$  tests utilize a metabolic cart. When a  $\text{VO}_{2\text{max}}$  test using a metabolic cart is attempted but none of the maximum value criterion are met, it is also labeled a  $\text{VO}_{2\text{peak}}$  test. However,  $\text{VO}_{2\text{peak}}$  tests that do not utilize a metabolic cart significantly reduces the equipment needs, trained personnel required, and subject discomfort, while still achieving a reliable measure of maximal aerobic capacity.

There are many cardiorespiratory protocols that measure  $\text{VO}_{2\text{peak}}$ , which include but are not limited to: the Bruce treadmill protocol (BTP), the Balke treadmill protocol, and the modified BTP. These protocols are designed to increase the intensity at a magnitude that is too difficult and rely on substantial increases in both speed and incline. These types of protocols are inappropriate for special populations due to the risk of injury and difficulty in completion (Stone, Lawlor, Nolan, & Kenny, 2011; Wampler et al., 2007; Winters-Stone et al., 2011).

For this reason, ergometry and cardiac specific protocols have been developed but also are not appropriate for the cancer population. Ergometry protocols rely on upper or lower body musculature to perform work at a certain cadence as resistance is increased. Cancer survivors often experience weakness, severe fatigue, and/or cachexia limiting strength (Berger, Gerber, & Mayer, 2012; Das et al., 2011; Fearon, 2011; Hayes et al., 2013; Schneider, Dennehy, Roozeboom, & Carter, 2002; Shapiro & Recht, 2001; Yeo et al., 2012). Ergometry protocols are often terminated due to an inability to pedal, which represents muscular weakness and fatigue, not aerobic capacity. Cardiac protocols such as the Naughton are less intense and progress more slowly than standard protocols, but often rely on an extended warm-up and long duration (Peel et al., 2009; Pina & Karalis, 1990; Watchie et al., 1986). Due to treatment-related toxicities, many CS experience debilitating fatigue which limits their ability to perform longer duration aerobic activity (Burnham & Wilcox, 2002). Many patients are unable to sustain cardiovascular activities (such as walking) for the required warm-up duration or at the required initial speed, thus making a  $\text{VO}_{2\text{peak}}$  value unattainable or unreliable. For these reasons, another protocol

must be used to address the needs of CS, yet provide a reliable value of  $VO_{2peak}$ . The RMCRI treadmill protocol was created to address this need.

The RMCRI treadmill protocol increases speed and incline at a lower degree of intensity with shorter (one minute) stages, yet still yields an accurate  $VO_{2peak}$  value (Shackelford et al., 2012). The first stage and progression of the RMCRI protocol is manageable for patients with the severest of toxicities, starting at a speed of one mile per hour (mph) at a 0% incline, yet the total length of the protocol is long enough to allow the more fit patients to be measured. 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 (+2.0%), the incline is never increased by more than 1.0% per minute and speed is increased by 0.1 mph per minute for the majority of the test. The shorter stages allow patients to complete entire stages frequently, allowing clinicians to calculate  $VO_{2peak}$  from the highest intensities sustained when fatigue is achieved. Steady state heart rate may not be achieved due to the higher rate of increasing intensity.

Due to the fact that there are no current cancer-specific treadmill protocols, CS must use AH or cardiac population treadmill protocols to determine their  $VO_{2peak}$ . Cancer survivors who are suffering from treatment-related toxicities and side-effects may not be able to fully exert themselves on these protocols due to the high intensities and durations required. Without a valid and accurate  $VO_{2peak}$  value, CS may be incorrectly evaluated, negatively altering their prescription of exercise and subsequent exercise intervention. The development of the RMCRI treadmill protocol is intended to be a cancer-specific protocol to determine  $VO_{2peak}$  in CS. Due to its low intensity progression, it allows patients to advance longer into the test, resulting in greater values. However, outside of

pilot data conducted at our facility, to our knowledge, there have been no other cancer-specific treadmill protocols evaluated for their validity. Specifically, there are no current studies that have examined the validity of the RMCRI protocol



## **CHAPTER II**

### **REVIEW OF LITERATURE**

#### **Introduction**

Cancer is the second leading cause of death in the United States, and it may account for approximately 1,600 deaths per day. Although prostate and breast cancer are the most prevalent for males and females, respectively, there are hundreds of different types of cancer, with lung and bronchus accounting for the greatest amounts of cancer deaths (ACS, 2015). However, due to advancements in cancer treatment, the 5-year survival rate for all-site cancers diagnosed between 2003 and 2009 has been reported to be at 68%, which is up from the survival rate of 49% between the years of 1975-1977 (ACS, 2015). Early detection and advanced treatments are resulting in longer life spans for CS. Nevertheless, cancer treatment-related side effects oftentimes negatively and severely affect a cancer survivor's overall health and well-being, which highlights the importance of improving an individual's quality of life (QOL), fatigue, depression, and physiological variables such as muscular strength, muscular endurance, and  $VO_{2peak}$ .

Cancer itself can have many side effects on an individual, such as cancer cachexia or fatigue, but the side effects of cancer treatments can be just as devastating.

Chemotherapy and radiation have been observed to reduce a client's quality of life (QOL) (Dhillon et al., 2012), increase fatigue (Buffart et al., 2013), increase depression (Yeo et al., 2012), decrease physical function (Murnane et al., 2012), and cause

cardiovascular dysfunction (Schneider et al., 2007b; Smoot et al., 2012). For clinicians and researchers, it is their objective to try and alleviate these side effects with the ultimate goal of increasing a survivor's QOL. For this reason, establishing a cancer rehabilitation program in order to address these issues is warranted.

### **Fatigue in Cancer Survivors**

Cancer-related fatigue (CRF) is one of the most common and prevalent side effects experienced by survivors. It can be defined as a clinical entity that is described by tiredness to exhaustion that is not precipitated by activity, or if it occurs after activity, it is out of proportion to the level of exertion (Berger et al., 2012). Bed rest has not been indicated to alleviate this type of fatigue, and it may actually worsen with physical inactivity. It has been reported that 58-94% of breast CS experience some aspect of fatigue during treatment, while 56-95% may have fatigue once they have completed treatment (Berger et al., 2012). In similar reports, it has been claimed that fatigue is experienced in 70-100% of CS (Cramp, 2012). Cancer-related fatigue can persist for months or even years after treatments have been completed, and can affect an individual physically, mentally, and emotionally. It has been cited that fatigue in cancer patients has been significantly higher than fatigue in the general public ( $p < 0.05$ ), and that severe fatigue in cancer patients was greater than fatigue experienced by 95% of a AH control group (Stone & Minton, 2008). In a similar study, it was observed that fatigue in survivors who did not have any type of rehabilitation after treatment worsened (Hayes et al., 2013). Overall fatigue will negatively affect a patient thereby leading to a decrease in QOL.

Although fatigue can affect psychological well-being, it may also severely impair physical functioning such as self-care actions, mobility, and any recreational activity. Of great concern, it has been reported that 91% of those who underwent chemotherapy stated that fatigue had changed their ability to perform daily activities, such as preparing food, cleaning, light lifting, and basic social activities (Hofman, Ryan, Figueroa-Moseley, Jean-Pierre, & Morrow et al., 2007). Others have looked at how fatigue directly altered physical functioning by using an objective measure, such as the time it takes for an individual to rise from his or her chair. It has been reported that survivors who had more fatigue had overall poorer physical functioning and took longer to rise out of a chair (Brown, McMillan, & Milroy, 2005). In a similar setting, researchers have witnessed an inverse relationship between self-reported fatigue and overall physical functioning (Mallinson, Cella, & Cashy, 2006). It is generally accepted that these impairments in physical functioning could be attributed to CRF.

### **Cardiovascular Dysfunction**

Cardiovascular function is one of the best ways of determining an individual's overall fitness. However, a disease such as cancer can drastically alter a survivor's cardiovascular capabilities and health. This may be due to the cancer itself, cancer treatments, deconditioning, age of patient at diagnosis, or any combination of these. Treatments with certain types of chemotherapy may result in cardiomyopathy, congestive heart failure, cardiotoxicities, and cardiovascular dysfunction (Doyle, Neugut, Jacobson, Grann, & Hershman, 2005; Gibson, Greufe, Hydock, & Hayward, 2013; Hayward, Hydock, Gibson, Bredahl, & Parry, 2013; Hydock, Wonders, Schneider, & Hayward, 2009; Smoot et al., 2012; Vejpongsa & Yeh, 2014).

Due to the many cardiovascular complications seen with cancer and cancer treatment, cardiovascular fitness in this population is often lower than age-matched AH populations. It has been demonstrated that  $VO_{2peak}$  can significantly differ between CS and the healthy population, specifically with CS consistently showing 30% lower  $VO_{2peak}$  values than apparently healthy age-matched control groups (Smoot et al., 2012). Not only were the survivors' values lower than the AH, but their overall classification fell in the 30<sup>th</sup> percentile in the published healthy female age-matched norms, which is also categorized as "poor" (ACSM, 2013; Heyward & Gibson, 2014). These findings suggest that CS will have an overall lower cardiovascular fitness level and may struggle on cardiorespiratory fitness protocols. It also supports the notion that survivors need rehabilitation after any type of cancer treatment to regain their cardiovascular fitness.

Cancer treatments have advanced significantly in the past years with adjuvant and targeted therapies. However, many studies have shown that treatments such as chemotherapy may lead to cardiomyopathy and cardiovascular toxicities, which in turn negatively affect cardiovascular function (Cardinale et al., 2010; Doyle et al., 2005; Hayward et al., 2013; Schneider et al., 2002; Schneider et al., 2007b; Vejpongsa & Yeh, 2014). Chemotherapy has been known to cause cardiotoxicity by reducing left ventricular ejection fraction, increasing time to peak filling of the left ventricle, and reducing stroke volume and cardiac output, which ultimately compromises oxygen and nutrient delivery to the body (Monsuez, Charniot, Vignat, & Artigou, 2010; Schneider et al., 2007b). It has been noted that >50% of patients who experienced congestive heart failure had a 30% reduction in left ventricular ejection fraction, which has been reported to severely compromise cardiovascular function (Swain, Whaley, & Ewer, 2003). The

most common chemotherapies include but are not limited to: alkylating agents, antimetabolites, topoisomerase inhibitors, mitotic inhibitors, and anthracyclines (ACS, 2015). These drugs will either damage, inhibit, or alter DNA to prevent cancer cells from reproducing.

Anthracyclines, such as Doxorubicin (DOX), are one of the most effective types of chemotherapy used to treat malignant cancers; however, they are also the most cardiotoxic. Cardiotoxicity has been reported to occur following repeated bouts of dose-dependent anthracycline administration, which has been speculated to be a function of cardiomyocyte apoptosis, oxidative stress, and/or disruption of myofibrils and contractile proteins (Richard et al., 2011; Eschenhagen et al., 2011). Repeated exposure to anthracyclines may lead to cardiotoxicity months or even years after treatment, but acute cardiotoxicity can occur minutes after administration (Arola et al., 2000; Jantunen, Vanninen, & Hartikainen, 2002; Monsuez et al., 2010; Vejpongsa & Yeh, 2014; Shakir & Rasul, 2009;). These cardiotoxicities may develop into cardiomyopathy or congestive heart failure (CHF) once treatment is completed (Monsuez et al., 2010; Hydock et al. 2009, Shapiro & Recht, 2001). It has been suggested that patients treated with DOX were 2.5 times more likely to develop cardiomyopathy than untreated clients (Doyle et al., 2005). Additionally, CS who received treatment had a 4.1% incidence rate of developing cardiomyopathy, while those who did not receive chemotherapy had only a 1.6% incidence rate. However, after a five-year follow-up the incidence rate increased to 5.0% and 10.2% for those who did not receive treatment and for those who did, respectively (Doyle et al., 2005). It has also been reported that 7% of patients develop CHF after a cumulative dose of 550 mg/m<sup>2</sup> of DOX, and it has been proposed that there is

a continuum of increasing risk for CHF with accumulation of dosage (Swain et al., 2003). Those who have a cumulative dosage of 400 mg/m<sup>2</sup>, 550 mg/m<sup>2</sup>, and 700 mg/m<sup>2</sup> of anthracyclines had a 3-5%, 7-26%, and 18-48% risk of developing CHF, respectively (Swain et al., 2003; Von Hoff et al., 1979).

Cardiac dysfunction has been researched extensively in animal studies as well. In the rat model, cardiac dysfunction has been compared between sedentary rats with no DOX treatment and sedentary rats injected with DOX. Rats that were administered DOX experienced a significant decline in left ventricular developed pressure (-59%), maximal rate of left ventricular pressure development (-43%), and a 45% increase in lipid peroxidation ( $p < 0.05$ ) (Wonders, Hydock, Schneider, & Hayward, 2008). When compared to control rats, DOX-treated rats experienced significantly lower left ventricular force production ( $p < 0.01$ ), increased myocardial oxidative stress markers, and altered transcript levels for all measured markers of cardiac remodeling, except for vascular endothelial growth factor-A ( $p < 0.001$ ) (Richard et al., 2011). It's also been observed that DOX administration in small doses over days or weeks has resulted in better survival rates than rats who were given a larger single dose of DOX (Hayward & Hydock, 2007).

### **Pulmonary Dysfunction with Cancer Treatments**

The assessment of pulmonary function allows clinicians to evaluate the damage done to the lungs and pulmonary system due to cancer or treatments. Pulmonary toxicity may be acute or chronic, and may persist many years after treatment (Schneider et al., 2002). Radiation or a combined modality with chemotherapy has led to obstructive and restrictive lung defects as well as decreased forced vital capacity (FVC), decreased forced

expiratory capacity (FEV1), and impaired diffusion capacity (Beinert et al., 1996; Eisbruch et al., 2002; Horning, Adhikari, Hoppe, & Olshen, 1994; Jensen, Carlsen, Groth, & Nissen, 1990; Lehne, Johansen, & Fossa, 1993; Lund et al., 1995). Treatments may cause pulmonary fibrosis and unusual development of pulmonary tissue, as well as radiation pneumonitis in patients who have undergone treatment for lung cancer. This occurs in 5-15% of patients receiving external beam radiation, and the overall risk of radiation pneumonitis was 7.8% in those who underwent combined modality therapy for lung cancer (Carver et al., 2007). Chemotherapy combined with radiation increases the chance of radiation pneumonitis to 11% ( $p = 0.001$ ) (Carver et al., 2007), and the two year risk of interstitial pneumonitis has been seen to be 26.8% (Granena et al., 1993). Chemotherapy alone has also been observed to damage the diaphragm directly (Whitney & Sporn, 2014).

In animal models, cancer and cancer treatments have resulted in respiratory muscle dysfunction. In cancer cachectic mice, mitochondrial respiratory chain complexes and oxygen consumption have been found to decrease in both the diaphragm and the gastrocnemius (Fermoselle et al., 2013). Similarly, all diaphragm muscle fiber types have been observed to atrophy, experience weakness, and compromise ventilation due to cancer cachexia in mice models (Roberts et al., 2013). Treatments such as DOX can negatively affect respiratory muscles, as it has been found that DOX significantly decreased diaphragm force as well as stimulate tissue inflammation and muscle fiber injury in the mouse model (Gilliam, Moylan, Callahan, Sumandea, & Reid, 2011).

Damage to the pulmonary system may directly affect cardiovascular function thereby reducing fitness. Cardiorespiratory fitness is an indicator of the ability to

transport and utilize oxygen, but these results may be affected if the pulmonary system is compromised. Because oxygenated blood is pumped back to the heart via the lungs, lack of sufficient oxygen due to pulmonary dysfunction will affect cardiovascular fitness. Common respiratory symptoms include wheezing, dyspnea, shortness of breath due to wheezing, overall shortness of breath, and shortness of breath when in a hurry (Myers et al., 2005; Raber-Durlacher et al., 2012; Sarna et al., 2004). Additionally, these investigators found that out of 142 CS, 38% walked slower than people their age because of breathlessness, 32% had to stop for breath when walking, and 11% were unable to leave their house because they were so breathless. All of the aforementioned items will severely affect an individual's cardiovascular system and fitness level.

### **Importance of Physical Activity**

A combination of early detection and advancements in cancer treatments are leading to better prognoses in CS. However, side effects such as fatigue and decrements to the cardiovascular system may cause patients to become physically inactive which may in turn lead to cardiovascular complications (Jones et al., 2009; Lakoski et al., 2012). Cancer patients report a decrease in time spent for exercise once radiation treatments start and they were less likely to engage in strenuous activities (Murnane et al., 2012). In one study, physical activity decreased by 50% after undergoing surgery, radiation, and/or chemotherapy (Kim et al., 2006). The reduced physical activity and cardiorespiratory fitness could also be associated with functional dependence, a loss of energy, and possibly an increase in cardiovascular morbidity and mortality (Lakoski et al., 2012). About 70% of cancer patients do not meet the US national exercise recommendations, and 58% of prostate and breast CS engage in routine exercise after treatment (Blanchard,



Courneya, & Stein, 2008; Denmark-Wahefried, Peterson, McBride, Lipkus, & Clipp, 2000).

Other studies report physical inactivity in up to 75% of CS (Coups & Ostroff, 2004; Denmark-Wahnefried, Peterson, McBride, Lipkus, & Clipp, 2000) and 28-41% in breast CS (Pinto & Maruyama, 1999). Similarly, other researchers have stated that only 30-47% of survivors are meeting the daily physical activity requirement, and that the percentage of CS who were met ACSM's recommendations for physical activity (29.6%) was lower than those who did not have cancer (37%) (Blanchard, Courneya, & Stein, 2008). Interestingly, others have stated that long time breast CS were 42% more likely to perform vigorous physical activities than healthy controls, as well as 28% more likely than controls to meet physical activity recommendations (Bellizzi, Rowland, Jeffrey, & McNeel, 2005; Blanchard et al., 2010). This finding is encouraging because it suggests more survivors are incorporating physical activity into their daily lives.

Physical inactivity is a strong influencing factor of low cardiorespiratory fitness as well as cancer mortality, and may decondition skeletal muscles and impair cardiopulmonary function (Kim et al., 2006). Three weeks of inactivity can lead to a significant decrease in cardiac output, oxidative capacity,  $VO_{2peak}$ , and muscle cross sectional area (Saltin et al., 1968). There is also evidence to suggest that decrements in physical activity may be associated with cardiac events and potentially death in both men and women (Gulati et al., 2003). In fact, some researchers state that peak exercise capacity is one of the strongest predictors of the risk of death, and has been seen to be even more powerful than other established risk factors for cardiovascular disease (Greenland et al., 2010; Myers et al., 2002; Steg et al., 2012). Age can play a factor too,

as it has been observed that cardiorespiratory fitness decreases around 10% per decade of life (Eskurza, Donata, Moreau, Seals, & Tanaka, 2002; Fitzgerald, Tanaka, Tran, & Seals, 1997; Jones et al., 2009; Lakoski et al., 2012). In a particular study, thirty years of aging reduced  $\text{VO}_{2\text{peak}}$  about 20%, with physical inactivity accounting for as much as 40% of the decline (Jones et al., 2009).  $\text{VO}_{2\text{peak}}$  itself can be a predictor of mortality, as it has been reported that a  $1 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  advantage in  $\text{VO}_{2\text{peak}}$  was associated with a 10% lower cardiac mortality risk (Kavanagh et al., 2003). Also, three weeks of inactivity can result in approximately a 35% decline in  $\text{VO}_{2\text{peak}}$  (Peel et al., 2009). What is most disconcerting is that peak oxygen uptake seems to be lower after thirty days of bed rest than after thirty years of aging (McGuire et al., 2001). On the Framingham risk score (FRS), which is an equation that estimates the ten year cardiovascular risk of an individual, it is stated that every one metabolic equivalent (MET) decrease in the FRS was associated with a 9% increased risk of death ( $p < 0.001$ ) (Gulati et al., 2003).

The importance of increased physical activity has been well documented. An ACSM roundtable of experts in cancer and exercise deemed that physical inactivity should be avoided at all costs (Schmitz et al., 2010). Cancer survivors who regularly exercise or who are physically active during or after treatments have significantly better physical functioning, cardiorespiratory fitness, psychological well-being, and QOL compared to those who did not (Brown et al., 2010; Dimeo et al., 1997; Murnane et al., 2012). In a study of 260 breast CS, a significant correlation between physical activity and cardiorespiratory fitness was observed ( $r = 0.35$ ,  $p < 0.01$ ), stating that more physically active clients had better their cardiovascular function (Taylor et al., 2010). Individuals who engage in regular physically active and have greater cardiorespiratory

function have a greater life expectancy as well (Blair et al., 1989; Blair et al., 1995; Kannel, Wilson, & Blair, 1985; Peel et al., 2009). Every one MET increase in exercise capacity has been related to a 12% improvement in survival, as well as a 17% decrease in mortality risk on the Framingham risk score (Gulati et al., 2003; Myers et al., 2002). It has been observed in CS that simply walking for one hour per week improved survival over those who were physically inactive, and that walking for 3 hours per week was associated with a decreased risk of mortality (Holmes, Chen, Feskanich, Kroenke, & Colditz, 2005). Physical activity of greater than three hours has shown benefits as well, as the 5-year survival rate for those who engage in 3 to 8.9 hours and >9 hours of physical activity was 93% and 97%, respectively (Holmes et al., 2005).

Although any amount of physical activity is beneficial, there are claims that physical activity only offers protective benefits when the intensity is at eight METs or greater (Peel et al., 2009). The same researchers claimed that women with an exercise capacity less than eight METs had nearly a threefold higher risk of dying than those with higher MET values. Additionally, in a study where CS were divided into an exercise or sedentary group for sixteen weeks, it was observed that physical activity levels did not differ between the two groups. However, only the exercise group showed a within-group significant increase in voluntary activity and energy expenditure, as well as a decrease in sedentary activity (Kim et al., 2009). Although some researchers believe there is a minimum intensity at which physical activity is beneficial, all agree that some physical activity is better than no physical activity.

### **Benefits of Exercise on Cancer Related-Fatigue and Cardiopulmonary Function**

Exercise has been demonstrated to improve psychological factors such as cancer-related fatigue (Schmitz et al., 2010; Schneider et al., 2007b; Yeo et al., 2012). Following a six-month exercise program that included individualized cardiorespiratory, strength, and flexibility training, survivors who were both in and out of treatment saw reductions in overall fatigue (Schneider et al., 2007b). Decreases in fatigue have ranged from -32 to -39% and -33 to -39% during and following treatment, respectively (Schneider & Hayward, 2013). However, it has been suggested that patients who are currently receiving treatment may see the largest improvements in fatigue, while those who had recently finished treatment should have longer durations between treatment and exercise initiation, and adhere to a shorter exercise program length (Puetz & Herring, 2012). Regardless, the investigators concluded that exercise may be a factor in the reduction of fatigue in clients both in treatment and following treatment. Various non-traditional types of exercise interventions have also been implemented with success. When exercise was prescribed over the phone to survivors for six weeks, a decline in fatigue was observed (Hayes et al., 2013). It was deemed that even if a survivor couldn't see an exercise physiologist face-to-face, indirect verbal communication was effective in improving fatigue.

In recent meta-analyses, it has been concluded that exercise interventions, whether it be face-to-face or over the phone, successfully reduced fatigue variables when compared to a sedentary control group (Brown et al., 2010; Carayol et al., 2013; Puetz & Herring, 2012). It has been proposed that 90-120 minutes of weekly moderate physical exercise is efficacious in reducing fatigue (Carayol et al., 2013). Cardiorespiratory

exercise has provided some of the greatest reductions in fatigue, as have moderate intensity resistance training programs (Brown et al. 2010; Burnham & Wilcox, 2002; Carayol et al., 2013; Cramp & Byron-Daniel, 2012). Interestingly, in a study where home-based exercises were performed by CS, fatigue was not significantly reduced compared with sedentary controls. It was also stated that no intervention type (supervised resistance training, supervised aerobic training, or home-based training) offered a significant advantage over another in reducing fatigue (Velthuis, Agasi-Idenburg, Aufdemkampe, & Wittink, 2010). Similarly, a review of literature revealed that while aerobic exercise has been reported to significantly reduce fatigue levels amongst CS, resistance training and alternative forms failed to reach significant improvements (Cramp & Byron-Daniel, 2012). Despite conflicting research, exercise has been shown to diminish fatigue to varying degrees.

The cardiorespiratory system may improve in CS undergoing treatment as a result of exercise. Aerobic exercise may reduce the risk of heart disease and protect the heart against injury caused from oxidative stress, which in turn can help offset some of the negative cardiovascular side effects caused by treatments. In fact, in those receiving adjuvant therapy, exercise was capable of significantly reducing survivors' resting heart rate and resting systolic blood pressure (SBP) (Dimeo et al., 1997; Schneider et al., 2007b). Additionally, it has been observed that exercise improved cardiac output, stroke volume, and increased arteriovenous oxygen differences, which may have led to an increase in functional capacity in these CS (Kim et al., 2006; Schneider et al., 2007b). Whole-body exercise has been shown to be efficient in attenuating chemotherapy-induced cardiotoxicity in CS, which accentuates the importance of exercise interventions

during treatment (Schmitz et al., 2010). A common deleterious symptom of cardiotoxicity is a shift in cardiac myosin heavy chain (MHC) isoform from  $\alpha$  to  $\beta$ . These isoforms encode cardiac muscle-specific proteins involved in force generation (Molkentin, Jobe, & Markham, 1996). In a study where rats treated with DOX remained sedentary or were allowed 24-hour access to voluntary wheel running cages, expression of cardiac  $\beta$ -MHC was  $43 \pm 7\%$  of the total MHC isoform while it was only  $24 \pm 4\%$   $\beta$ -MHC isoform in exercised animals (Hydock et al., 2009). This exercise-induced preservation of MHC isoform distribution was associated with a maintenance of cardiac function. Similarly, it has been reported that even a single bout of acute endurance exercise twenty-four hours before the administration of DOX has a cardioprotective effect. This single bout of exercise decreased end systolic pressure, left ventricular developed pressure, and the maximal rate of left ventricular pressure development (Wonders et al., 2008). Correspondingly, rats who performed an acute bout of exercise before DOX administration were able to reduce the amount of myocardial oxidative damage and dysfunction (Ji & Mitchell, 1994). Acute exhaustive exercise after DOX administration also increased the survival rate of rats (Combs, Hydman, & Bonner, 1979). This supports the concept that exercise before or after treatment may attenuate cardiotoxicity.

Pulmonary function can be improved due to exercise, as shown by increases in percent of predicted forced vital capacity, forced expiratory volume, and overall lung function in both during and after treatment (Marulli et al., 2010; Schneider et al., 2007b). It has been observed that regular exercise strengthens the respiratory muscles and will improve cellular respiration, as well as improving the respiratory, muscular and

cardiovascular systems (Zolaktaf, Ghasemi, & Sadeghi, 2013). Additionally, respiratory and pulmonary rehabilitation that includes aerobic and muscular endurance training, has shown to improve QOL and exercise tolerance in those with chronic obstructive pulmonary diseases (Nici et al., 2006). It's also been observed that pulmonary rehabilitation that includes low-intensity endurance and strength training has resulted in a reduction of expiratory flow limitations as well as hyperinflation of the lungs at rest (Yoshimi et al., 2012).

### **Benefits of Exercise on Exercise Capacity and Peak Volume of Oxygen Consumption**

Cardiorespiratory fitness is a reflection on the overall fitness of the body, with  $VO_{2peak}$  being a primary variable used to assess the cardiovascular system. With CS, an exercise intervention is used to increase this variable along with many others, such as physical performance. Baseline  $VO_{2peak}$  measures are generally higher in those who are physically active than those who are sedentary (Bruce, Kusumi, & Hosmer, 1973; Watchie et al., 1986). For those that perform weekly physical activity,  $VO_{2peak}$  has been seen to significantly increase compared to those who do not (Kim et al., 2006; Marulli et al., 2010; May et al., 2010). A recent meta-analysis stated that aerobic exercise successfully increased CS'  $VO_{2peak}$  when compared to sedentary control groups (Jones et al., 2011), where improvements in  $VO_{2peak}$  have varied from 2 to 40% (Garner & Erck, 2008; Jones et al., 2011; Kim et al., 2006; Klika, Callahan, & Drum, 2009; Marulli et al., 2010; McNeely et al., 2006; Schneider et al., 2007b). The improvements in  $VO_{2peak}$  may vary depending on the type of exercise intervention or on individual survivor characteristics. Physical exercise can also improve the performance on an aerobic test, such as increased treadmill time (Dimeo et al., 1997; Schneider et al., 2007b; Sprod,

Hsieh, Hayward, & Schneider, 2010). Specifically for clients who were both in and out of treatment, treadmill time has been seen to increase from baseline to post assessments by as much as 28% (Schneider et al., 2007b).

### **Cancer Rehabilitation Programs**

With advancements in diagnosis and treatments for cancer, survival rates are at an all-time high. However, treatments are leaving CS with side effects such as fatigue, depression, and reduced QOL. In 1970, the National Cancer Act was passed to aid federal efforts in fighting cancer. It created the National Cancer Program, which is directed by the National Cancer Institute. In doing so, the act has funded thousands of researchers and programs in hospitals and other medical facilities in every state to improve cancer diagnosis, treatment, and care. However, due to earlier detection, advanced treatments, and improvements in technology, hospital and postoperative based rehabilitation programs virtually disappeared over the years (Alfano, Ganz, Rowland, & Hahn, 2012). Today, with over 1.6 million new diagnoses of cancer to be expected, the need for cancer rehabilitation is receiving attention once again (ACS, 2015).

The need for cancer rehabilitation has been researched by mailing surveys to CS. Surveys have addressed satisfaction of current rehabilitation services as well as services and factors that were unmet. The most sought service that was currently unavailable was physical therapy, followed by physical training, psychological counseling, and occupational therapy. It was reported that 63% surveyed conveyed a need for at least one of the aforementioned services, while 40% stated that none of their rehabilitation needs were being met (Thorsen et al., 2011). Similar studies show that 75-85% of cancer



patients are interested in physical activity counseling (Jones & Courneya, 2002; Stevinson et al., 2009).

Different organizations such as the American College of Sports Medicine (ACSM), American Cancer Society (ACS), and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) have established physical activity guidelines for CS. Cancer rehabilitation programs are slowly starting to form in hospitals and businesses such as the Young Men Christian Association's (YMCA) gymnasiums, but most do not have a model program to assist survivors. Programs need to be carefully structured and rigidly controlled where all patients should be assessed and reassessed to evaluate progress.

A clinical program should have designed interventions structured to address and treat the following toxicities: cardiovascular, pulmonary, gastrointestinal, musculoskeletal, immune, hematological, and neurotoxicity (Schneider et al., 2002). Established programs should aim to provide scientifically based individualized prescriptive exercises for patients, provide ongoing basic and clinical research for alleviating cancer related symptoms, and advance educational preparation and professional development to promote high standards for cancer rehabilitation. The Rocky Mountain Cancer Rehabilitation Institute (RMCRI) is an established clinic that has all the necessary tools and protocols to address the aforementioned goals. Additionally, research conducted at RMCRI has shown that exercise interventions in CS provide significant improvements in functional capacity, resting heart rate, time on treadmill, FVC, range of motion, muscular strength and endurance,  $VO_{2peak}$ , and psychological well-being (Schneider & Hayward, 2013; Schneider et al., 2007a; Schneider et al., 2007b;

Schneider, Dennehy, & Carter, 2003; Schneider et al., 2002; Schneider, Stephens, Quick, & Carter, 2000; Sprod et al., 2010). With the increased need of structured cancer rehabilitation programs, there is a need for accurate assessments and exercise prescriptions to document changes in a cancer survivor's overall health. An accurate measure of maximal volume of oxygen consumed during exercise is an excellent indicator of overall health (Jones et al., 2011; Jones et al., 2005; McNelley et al., 2006).

### **Clinical Maximum Volume of Oxygen Consumption Assessment**

The term maximum volume of oxygen consumed ( $\text{VO}_{2\text{max}}$ ) can be defined as an individual's maximum oxygen consumption ( $\text{VO}_2$ ) during maximal work. The ability to deliver oxygen to metabolically active skeletal muscles and other systems of the body for ATP re-synthesis is an essential need for humans.  $\text{VO}_2$  increases proportionally to exercise intensity. When oxygen consumption increases, it is dependent on the total amount of blood pumped by the heart and is redistributed to the working muscles (Smith & Fernhall, 2011). Greater measures of  $\text{VO}_2$  have been associated with reduced all-cause and cancer mortality (Gulati et al., 2003; Myers et al., 2002; Sawada et al., 2003; Kavanagh et al., 2003).  $\text{VO}_{2\text{max}}$  can be expressed in absolute terms (L/min) or in relative terms ( $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ). Absolute  $\text{VO}_2$  provides a measure of energy cost on non-weight bearing activities such as cycling or arm ergometry (Heyward & Gibson, 2014). In most instances,  $\text{VO}_2$  is conveyed relative to an individual's body weight in kilograms (kg), which allows clinicians to compare individuals of different body masses, as well as calculate energy cost of weight bearing activities (walking, running). Relative  $\text{VO}_2$  is expressed in  $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  and measures the amount of oxygen that is consumed per

kilogram of body weight every minute. The resting relative  $\text{VO}_2$  is about  $3.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , which is equivalent to one MET.

The measurement of  $\text{VO}_{2\text{max}}$  has been deemed the most valid representation of oxygen consumption (Brooks et al., 2005; Hawkins et al., 2006; Heyward & Gibson, 2014; Jones et al., 2008; Kim et al., 2006). Typically a  $\text{VO}_{2\text{max}}$  test uses GA via a metabolic cart to measure the participant's oxygen consumption. However, to do a valid and reliable  $\text{VO}_{2\text{max}}$  test, one needs the proper equipment and personnel for accurate results. Also, a true  $\text{VO}_{2\text{max}}$  test requires the patient to exercise until complete exhaustion (plateau in  $\text{VO}_2$ ,  $\text{RER} > 1.15$ , blood lactate  $> 8 \text{ mmol}$ ), which may be dangerous or even impossible for some. Factors such as the expense of the equipment, the lack of trained personnel, physical limitations, lack of motivation, persistent fatigue, and impact on a patient may not make a  $\text{VO}_{2\text{max}}$  test feasible or valid for special populations (Jones et al., 2008; Pina & Karalis, 1990; Stone et al., 2011).

Due to the strict criteria that must be met in order to establish a reliable and valid  $\text{VO}_{2\text{max}}$ , a  $\text{VO}_{2\text{peak}}$  test is often used instead.  $\text{VO}_{2\text{peak}}$  is an objectively measured variable and can be defined as the highest  $\text{VO}_2$  achieved during an exercise test, typically via a metabolic cart (Heyward & Gibson, 2014; Jones et al., 2011; Pina & Karalis, 1990;).  $\text{VO}_{2\text{peak}}$  tests are often shorter due to termination criteria, require less equipment, less effort, and yield similar results to  $\text{VO}_{2\text{max}}$  tests. In fact, it has been observed that there are no significant differences in final  $\text{VO}_2$  values between a  $\text{VO}_{2\text{peak}}$  and a  $\text{VO}_{2\text{max}}$  test (Day, Rossiter, Coats, Skasick, & Whipp, 2003; Eldridge, Ramsey-Green, & Hossack, 1986; Hawkins et al., 2006; Howley, 2007; Jones et al., 2011). During a peak test, the subject pushes to what they perceive as maximal effort or exhaustion instead of equipment

determining whether they reached physiological exhaustion. However, many of the peak  $\text{VO}_2$  tests are geared towards the healthy populations, not the cancer population. Less intense protocols would be beneficial and more accurate for those who have undergone or are currently undergoing cancer treatment and are suffering from the deleterious side effects.

### **Validity of Maximum Volume of Oxygen Consumption Assessments**

GA have been considered to be the gold standard for measuring  $\text{VO}_2$  because of the direct measurement of oxygen consumption (Waddoups, Wagner, Fallon, & Heath, 2008). This type of analysis uses a respiration mask that is connected to a metabolic cart. The metabolic cart is capable of directly measure the amount of oxygen ( $\text{O}_2$ ) consumed, the amount of carbon dioxide ( $\text{CO}_2$ ) expelled, and the respiratory exchange ratio (RER). The RER is the ratio of the amount of  $\text{CO}_2$  expelled compared to the amount of  $\text{O}_2$  consumed. It may also measure ventilation and other pulmonary values as well. However, due to the expenses of obtaining a metabolic cart, predictive  $\text{VO}_2$  equations have been used to estimate  $\text{VO}_{2\text{max}}$ . These equations have been deemed accurate as long as the  $\text{VO}_2$  protocol is valid and reliable, and may vary depending on whether the test is a submaximal, maximal, or peak test (ACSM, 2013). Submaximal  $\text{VO}_2$  tests generally end at a pre-determined stopping point (% heart rate max/heart rate reserve). Submaximal tests have been found to be a feasible alternative to maximal tests and ultimately look to estimate an individual's  $\text{VO}_{2\text{max}}$  (May et al., 2010; Heyward & Gibson, 2014). Specific walking and running equations developed by ACSM are used in many  $\text{VO}_{2\text{max}}$  prediction equations and accurately predict energy expenditure when steady state  $\text{VO}_2$  is achieved (Hall, Figueroa, Fernhall, & Kanaley, 2004). The relationship between measured

submaximal  $\text{VO}_2$  and ACSM prediction equations has been seen to be 0.92 (Bader, Maguire, & Balady, 1999).

Some of the most common treadmill protocols include but are not limited to: the BTP, the modified BTP, and the Balke. The BTP has been validated as an accurate measurement of  $\text{VO}_{2\text{max}}$  and is one of the most used treadmill protocols (Akinpelu et al., 2014). ACSM's walking and running equations are used in the multi-stage model  $\text{VO}_2$  prediction equations for a submaximal BTP (Heyward & Gibson, 2014; ACSM, 2013). It has been reported that the correlations between Bruce's predicted  $\text{VO}_{2\text{max}}$  and the observed  $\text{VO}_{2\text{max}}$  was 0.94 in patients without cardiac conditions and 0.87 for men with cardiac disease (Bruce, Kusumi, & Hosmer, 1973). However, this test includes drastic increases in both speed and incline, which might not be suitable for the cancer population. Research suggests that protocols with larger increments between stages result in an overestimation of  $\text{VO}_{2\text{peak}}$  and show greater variability (Bader, Maguire, & Balady, 1999). Similarly, Bruce estimations of  $\text{VO}_{2\text{max}}$  have been overestimated by  $4 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  in sedentary groups (Pollock et al., 1982), while others have been seen to significantly underestimate the prediction of  $\text{VO}_{2\text{max}}$ . It's been stated that the prediction equations would be most valid in average to above average fitness populations who are between 20 and 40 years of age (Pollock et al., 1982).

Due to the difficulty of current protocols, less intense protocols such as the modified BTP and Balke may be more appropriate for high risk clients. The exercise intensity of the modified BTP does not increase as drastically as the BTP, and can calculate estimated  $\text{VO}_{2\text{max}}$  by using ACSM's walking/running equations (Heyward & Gibson, 2014; ACSM, 2013). The Balke treadmill protocol estimates  $\text{VO}_{2\text{max}}$  through

equations as well, and has been found to have a correlation of 0.92 between predicted and actual  $\text{VO}_{2\text{max}}$  (Pollock et al., 1976; Pollock et al., 1982). Other protocols such as, but not limited to, the United States Air Force, modified Balke, Naughton, modified Naughton, and Balke-Ware protocols have also shown high correlations with observed  $\text{VO}_{2\text{max}}$  (ACSM, 2013; Balke & Ware, 1959; Naughton & Nagle, 1965; Patterson, Naughton, Pietras, & Gunnar, 1972; Wolthuis et al., 1997).

There have been both similarities and discrepancies when correlating  $\text{VO}_{2\text{max}}$  values between different protocols. The modified BTP and Naughton protocols have been found to produce a similar  $\text{VO}_{2\text{peak}}$  in cardiac patients as well as detecting ischemic abnormalities (Handler & Sowton, 1984; Naughton & Nagle, 1965; Strzelczyk, Cusick, Pfeifer, Bondmass, & Quigg, 2001;). However, other studies have observed that the Naughton protocol was not suitable for some elderly individuals due to the exhaustion caused by the protocol, while the BTP was more efficient and obtained the largest number of diagnostic tests with a significantly lower number of inconclusive tests (Aguilar et al., 1997; Strzelczyk et al., 2001). When comparing the Balke to the BTP, the Balke produces slightly lower  $\text{VO}_{2\text{max}}$  values that are statistically non-significant (McArdle, Katch, & Pechar, 1973; Moody, Kollias, & Buskirk, 1969; Pollock et al., 1982). When compared to the modified BTP, the Bruce treadmill protocol elicits higher physiological stress variables such as heart rate, blood pressure, and capacity of peak exercise (Trabulo, Mendes, Mesquita, & Seabra-Gomes, 1994). Interestingly, some have suggested that a modified BTP is unnecessary because any patient can undergo testing with a ramp protocol (Will & Walter, 1999).

As already stated, there have been high correlations found between  $\text{VO}_{2\text{max}}$  and  $\text{VO}_{2\text{peak}}$  tests (Day et al., 2003; Eldridge et al., 1986; Hawkins et al., 2006; Howley, 2007; Jones et al., 2011). Similarly, it has been suggested that submaximal testing does provide a reasonable alternative to  $\text{VO}_{2\text{max}}$  testing in CS (May et al., 2010). The relationship between  $\text{VO}_2$  attained via a submaximal test and predicted  $\text{VO}_{2\text{max}}$  during a ramp protocol was 0.92 (Bader et al., 1999), and a correlation of 0.96 was observed between observed  $\text{VO}_{2\text{max}}$  and estimated  $\text{VO}_{2\text{max}}$  in healthy individuals (Ebbeling, Ward, Puleo, Widrick, & Rippe, 1991). Although submaximal tests are feasible, it is still recommended that CS undergo an exhaustive exercise assessment before the start of an exercise program (May et al., 2010). Some have stated that the predictive validity of a submaximal test diminishes at the extremes of specified heart rate ranges (Waddoups et al., 2008). A submaximal BTP results in lower predictive  $\text{VO}_{2\text{max}}$  values and shows no significant correlation with a maximal BTP (Dabney & Butler, 2006). Another study found that there was only a moderate correlation between a  $\text{VO}_{2\text{max}}$  test and a submaximal test, whereas there was a high correlation between a  $\text{VO}_{2\text{max}}$  test and a steep ramp test (De Backer et al., 2007). The same authors concluded that the submaximal test produced invalid results, where the steep ramp protocol seems to be practical, reliable, and valid. Submaximal outcomes for loading capacity may be inaccurate and may not represent an individual's true  $\text{VO}_{2\text{max}}$ . It has also been reported that submaximal tests overestimated  $\text{VO}_{2\text{max}}$  in healthy subjects, and that submaximal tests seem to be of less value for training guidance in CS, and may have limited value in assessing the exercise capacity (De Backer et al., 2007).

Although the treadmill is one of the most common methods for testing for  $\text{VO}_2$ , other modes such as cycle ergometers may also be used. Cycle ergometer protocols are used to predict  $\text{VO}_{2\text{max}}$  in many clinical settings (De Lucas, Rocha, Burini, Greco, & Denadai, 2003; Fitchett, 1985; Vanderburg, 1993; Sport, Williford, Wang, Olson, & Blessing, 1993). However, there have been significant differences found in maximal data between cycle ergometer and treadmill protocols (Astrand & Rodahl, 1977; Moody et al., 1969; Pollock et al., 1982; Pollock, Dimmick, Miller, Kendrick & Linnerud, 1975). When compared to cycle ergometer protocols,  $\text{VO}_{2\text{max}}$  values have been 5 to 11% higher on the treadmill (Astrand & Rodahl, 1977; McArdle et al., 1973; Moody et al., 1969; Pollock et al., 1982). There has been only one study that shows similar findings in maximal heart rate (HR) between the two protocols (McArdle et al., 1973). Peak  $\text{VO}_2$  observed during the BTP has also been significantly higher than that on the cycle ergometer (Strzelczyk et al., 2001). Mean peak  $\text{VO}_2$  has been observed to be higher on both the BTP and the modified Naughton than on the bike. Interestingly, the BTP has been preferred over both the Naughton and cycle ergometer protocols (Strzelczyk et al., 2001). In a study where a submaximal YMCA cycle ergometer test and BTP were compared, predicted  $\text{VO}_{2\text{max}}$  was less on a cycle ergometer than it was for a maximal BTP (Dabney & Butler, 2006). In opposition to this finding, cycle ergometry has been moderately correlated with maximal exercise testing (De Backer et al., 2007). When CS performed a submaximal cycle ergometer test,  $\text{VO}_{2\text{max}}$  test, and a steep ramp test during an initial assessment and a reassessment, overall  $\text{VO}_{2\text{max}}$  values improved. Remarkably though, a significant improvement in  $\text{VO}_{2\text{max}}$  was only seen pre-to-post in the ramp test, not the cycle ergometer test (De Backer et al., 2007). Although differences between the



cycle and treadmill have been observed, when clients have adequate cycle training the results seem to equalize between the protocols (Pollock, Dimmick, Miller, Kendrick, & Linnerud, 1975).

### **Cancer Specific Cardiovascular Testing**

Cancer survivors can utilize established protocols such as the BTP to determine their  $VO_{2peak}$ , but the values may be inaccurate due to aforementioned factors. The BTP and Balke protocols were meant to be tested on AH populations. Additionally, the multi-stage model equations for the BTP are only valid when the test is a submaximal test due to steady state  $VO_2$  (Heyward & Gibson, 2014). There are population specific and generalized equations to estimate  $VO_{2peak}$  for the BTP, but they are only appropriate for active and sedentary genders, as well as cardiac and elderly persons (Foster et al., 1984; Foster et al., 1983; Heyward & Gibson, 2014; Pollock et al., 1982). None of the aforementioned categories exclusively include all CS. Since survivors do not fit in any of these classes, estimated  $VO_{2peak}$  through these equations may prove to be invalid or inaccurate.

To date there is no cancer-specific cardiovascular treadmill test. Cancer survivors experience many cancer and treatment-related side-effects and toxicities, such as ambulatory difficulties, peripheral neuropathy, balance difficulties, and neuromuscular dysfunctions, which may affect an individual's ability to achieve an accurate and valid  $VO_{2peak}$  (Wampler et al., 2007; Winters-Stone et al., 2011). Cancer survivors have a higher risk of injury due to falling than AH populations, (Stone et al., 2011; Winters-Stone et al., 2011) and established protocols such as the BTP increase in intensity too quickly and may be too difficult for CS to complete safely without risk of injury. Due to

this, established protocols may not be able to establish a safe, reliable, and valid  $VO_{2peak}$ . RMCRI established a treadmill protocol that was specifically developed for CS. Unlike most treadmill tests, the RMCRI protocol increases intensity at a low but effective rate. There are no drastic increases in incline like the BTP and no constant speeds that may be too fast for CS, observed in the Balke protocol. Instead, survivors are able to start off at a very low intensity and gradually work their way to a higher intensity. The smaller grades and lessened speeds accommodate any probable conditions caused by cancer treatments such as pulmonary, musculoskeletal, and cardiovascular dysfunctions. The goal of the RMCRI protocol is to have survivors reach  $VO_2$  values close to maximal without having to stop early due to factors other than cardiovascular function. No studies have been conducted which seek to establish and validate a treadmill protocol specifically for CS.

## **CHAPTER III**

### **METHODOLOGY**

#### **Subjects**

A total of 60 subjects participated, which was determined by a power analysis before the start of the study. Participants who are CS (n=45) were enrolled in the Rocky Mountain Cancer Rehabilitation Institute's cancer rehabilitation program. Inclusion criteria for cancer survivor subjects were 1) diagnosed with cancer, 2) at least 18 years of age, and 3) no history of stroke, chronic respiratory difficulties, or severe arterial hypertension (resting systolic blood pressure >200 mmHg, resting diastolic blood pressure 110, or both). The CS medical history were known by faxed medical records from the participant's oncologist or physician. Recruitment occurred by placing fliers detailing information about the study around the institute, as well as the head researcher talking to CS directly. Participants were explained that they will be partaking in a treadmill validation study, where they will perform three separate treadmill tests over the course of three weeks. Those who participate were offered three months of free training at RMCRI. If a cancer survivor had a question about the study, they were informed to ask the lead researcher.

Apparently healthy control subjects (n= 15) were referred from the local community and from the University of Northern Colorado's (UNC) campus. An email

that described the study was sent out to the entire College of Natural and Health and Sciences Department at UNC, asking for volunteers to participate. Fliers were also put up at local gyms and recreational centers. If a control subject was interested or had questions, they contacted the lead researcher. Apparently healthy control participants were required to fill out a Physical Activity Readiness Questionnaire (PAR-Q) to determine whether they were eligible to participate in physical exercise (see Appendix A). If a participant answered “yes” to any of the PAR-Q’s questions, that individual was not allowed to participate in the study. If a control subject was deemed capable to participate in physical activity, the subject was required to fill out a medical history form (see Appendix B). This medical form history evaluated pre-existing medical conditions that determined whether or not the participant met inclusion criteria. Inclusion criteria for the control subjects were 1) no history of cancer, 2) at least 18 years of age, 3) no history of stroke, chronic respiratory difficulties, or severe arterial hypertension (resting systolic blood pressure >200 mmHg, resting diastolic blood pressure 110, or both), and 4) have an answer of “no” to all PAR-Q questions.

Exclusion criteria for all subjects included 1) history of congestive heart failure, 2) history of myocardial infarction, 3) chronic lung disease, 4) asthma, 5) significant ambulatory issues, 6) history of coughing up blood, 7) fainting, 8) epilepsy, and 9) neuropathy in the lower extremities. Each protocol and test were explained in detail to each subject. Safety was ensured by having a minimum of three Cancer Exercise Specialists (CES) present during each test, each having his or her own responsibility. When each subject fully understood the study, each test and protocol, and the expectations for participation they signed an informed consent (see Appendix C) which

has been approved by the University of Northern Colorado's Institutional Review Board (see Appendix D).

### **Experimental Design**

The purpose of this study was to assess the construct validity of the RMCRI multi-stage treadmill protocol for a cancer-specific population against standard metabolic GA and the BTP. Participants who qualified for the study were randomly assigned an order of the three different protocols through a Statistical Analysis System (SAS) randomization code (SAS, 9.3). Three separate treadmill tests were performed over three weeks. A week of rest following each treadmill test was given to allow subjects to recover and reduce the risk of fatigue. Cancer survivor participants may have been currently receiving cancer treatments during the study. Therefore, if a CS was scheduled to perform a treadmill test within three days after a treatment, then that individual was allowed to perform their assigned  $VO_{2peak}$  test the following week. The following protocols were performed: a RMCRI  $VO_{2peak}$  test using gas analysis (RGAP), a  $VO_{2peak}$  Bruce treadmill protocol (BTP), and a RMCRI  $VO_{2peak}$  test without gas analysis (RWO GAP). Construct validity will be used to evaluate the RMCRI protocol. Construct validity refers to whether variables of a test or instrument accurately measures the variable that they are intended to measure. It was measured by comparing the variable achieved from the test or instrument being examined to the variable achieved from an established, reliable, and valid method. This was accomplished by accumulating evidence from correlation coefficients, ANOVA demonstrating differences between groups, pre-test and post-test interventions, and factor analyses. To calibrate the treadmill to ensure accuracy of speed, the length of the treadmill belt was measured. A

piece of tape was then be placed on the belt, and one piece of tape on the deck adjacent to the belt, and the treadmill was then set a particular speed. A researcher observed how long (seconds) it took to see 20 revolutions of that piece of tape. To determine the speed, the belt length was multiplied by the number of revolutions, and then divided by the time measured to complete the set of revolutions. This was then repeated for increments of 1mph from the range of 1 mph to 7 mph.

To ensure a CS was fit to complete a  $\text{VO}_{2\text{peak}}$  test, each CS was required to complete the Feeling Scale of Exercise Scale (see Appendix E) before every  $\text{VO}_{2\text{peak}}$  test. If a cancer survivor scored  $\leq -2$  then that individual was not allowed to attempt a  $\text{VO}_{2\text{peak}}$  peak test, and attempted the test the following week. Resting blood pressure (BP), heart rate (HR), and blood oxygen saturation ( $\text{SpO}_2$ ) was measured before each test, along with the subject's body weight (kg). Blood pressure was determined using manual auscultation, heart rate was determined using a Polar® heart rate monitor, and  $\text{SpO}_2$  was determined using a Clinical Guard ® pulse oximeter. During each test,  $\text{SpO}_2$ , HR, and rating of perceived exertion (RPE) was recorded. Certified Cancer Exercise Specialists (CES) conducted all treadmill tests to ensure safety. One CES was responsible for changing the grade and speed of the treadmill during the protocol and record all information during the test, a second measured BP, a third stood behind the treadmill to spot the subject, and a fourth set up and operated a metabolic cart when necessary. Unless a subject felt uncomfortable, CES's suggested that the participant not hold onto the handrails during the tests. If a subject choose to hold onto the handrails, they were required to hold onto them for the entirety of the test. Each participant was encouraged to exert themselves as close as possible to their perceived maximum effort. A test was

deemed a  $\text{VO}_{2\text{peak}}$  test if at least two of the following criteria were met: 1) subject terminated test due to self-reported maximal effort and fatigue, 2) highest heart rate achieved was within ten beats per minute of the individual's estimated heart rate max using the equation:  $208 - (0.7 * \text{age})$ , and 3) if a subject gave a RPE value on the modified Borg RPE scale of at least an eight. If at least two of these criterion were not met, the test results were not used.

Before each test began, the participants were given the following instructions: 1) one CES will be taking your blood pressure once every three minutes, 2) another CES will be recording all data from the test, as well as changing the speed and grades of the treadmill, 3) a pulse oximeter will be placed on your index finger, in which we will record your oxygen saturation at the end of every minute, 4) another CES 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's necessary, 7) regardless 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 lower your vitals close to resting measures.

Four different  $\text{VO}_{2\text{peak}}$  values were compared using a repeated measures ANOVA:

1)  $\text{VO}_{2\text{peak}}$  obtained from the RGAP via a metabolic cart, 2) estimated  $\text{VO}_{2\text{peak}}$  calculated from the last completed stage of the GA test using ACSM's walking/running equations (EVACSM), 3)  $\text{VO}_{2\text{peak}}$  peak from a peak BTP, and (4)  $\text{VO}_{2\text{peak}}$  calculated from a

RWOGAP.  $\text{VO}_{2\text{peak}}$  values from the GA test were compared with  $\text{VO}_{2\text{peak}}$  that was calculated from the last stage of the same test to determine whether the ACSM equations were valid in determining  $\text{VO}_{2\text{peak}}$ . The values from the BTP and GA were compared to determine whether the BTP yielded accurate values for CS. Finally, the GA values were compared to the values calculated from a separate RMCRI test without GA to determine whether the metabolic cart altered a cancer survivor's performance on a treadmill test.

### **Rocky Mountain Cancer Rehabilitation Institute Protocol**

The RMCRI treadmill protocol appears in detail in Table 1 and in Appendix F. There are 21 total stages, with each being only one minute long. Stage zero starts at 1 mph and a 0% incline. Speed will increase by no more than 0.5 mph from stage zero to stage six, and an incline of 2% will not be seen until stage four. Starting at stage six, speed will increase by 0.1 mph and grade will increase by 1% after every completed stage. Participants were explained that they will be performing a RMCRI  $\text{VO}_{2\text{peak}}$  treadmill test and that they may end the test whenever they deem necessary, but are encouraged to continue as far as physically possible.



Table 1

*Rocky Mountain Cancer  
Rehabilitation Protocol*

<b>Stage</b>	<b>Speed</b>	<b>Grade</b>	<b>Time</b>
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%	***

During the test, heart rate and SpO<sub>2</sub> were taken at the end of every minute. RPE and BP were taken at the end of every three minutes. Clients were encouraged to not use the handrails during the test, but if they felt uncomfortable or felt that the handrails are necessary then they were allowed. The test ended when the participant felt he or she had reached their maximum threshold of exertion on the treadmill and could not continue any further. The test also ended if any of the following criteria were met: HR did not increase with increased intensity, systolic blood pressure (SBP) did not increase with intensity, DBP oscillated more than 10 mmHg from resting measure, SpO<sub>2</sub> dropped below 80%, and/or verbal consent of the participant to end the test due to any safety issues.

Once the client reached his or her perceived maximal exertion, a cool down period was given in order for the client to return close to their resting measures. During the cool down, HR and SpO<sub>2</sub> were taken every minute, and RPE and BP was taken once every three minutes. Once values reached close to resting measures, and the client felt comfortable to get off the treadmill, the treadmill was stopped. Final HR was taken at the conclusion of the test, along with the time of duration and final completed stage.

American College of Sport Medicine walking and running equations were used to calculate VO<sub>2peak</sub> by using the last completed stage of the protocol. If the participant was walking at the termination point of the test, the following equation was used:  $VO_{2peak} = (0.1 \times S) + (1.8 \times S \times G) + 3.5$ . The variable S represents the speed of the treadmill expressed in meters/min, and G signifies the grade of the treadmill expressed in decimal format (%). Depending on how far a participant goes, the individual may be walking or running due to the speed and/or grade. The subject will determine whether they need to walk or run at the stage speed and incline. If a subject is holding onto the handrails and

walking at the termination of the test, the following correction equation was used:

$VO_{2peak} = 0.694 [(0.1 \times S) + (1.8 \times S \times G) + 3.5] + 3.33$ . If the subject was running when the test was terminated, the following equation was used:  $VO_{2peak} = (0.2 \times S) + (0.9 \times S \times G) + 3.5$ . If the subject was running at the end of the test while holding on to the handrails the following correction equation was used:  $VO_{2peak} = 0.694 [(0.2 \times S) + (0.9 \times S \times G) + 3.5] + 3.33$  (American College of Sports Medicine, 2013).

### **Bruce Protocol**

The BTP is shown in Table 2 and in Appendix G. This protocol consists of a three minute warm-up at 1.7 mph at a 0% grade, followed by seven different three minute stages where both the speed and grade will be increased at the completion of each stage. The first stage starts at 1.7 mph and 10% grade, where grade then increases by 2% every stage and speed increases from 0.5-0.9 mph, depending on the stage. Handrail usage criteria was identical to the RMCRI protocol guidelines. Each participant started with a three minute warm-up at a low intensity with 0% grade. Once the test began, HR, BP, and RPE were taken once every three minutes. The participant was instructed to go as far as he or she possibly could, exerting themselves to perceived maximum effort. Termination criteria was exactly the same as the RMCRI protocol. After exhaustion was achieved, a cool-down period was initiated. During this time, RPE, SpO<sub>2</sub>, blood pressure, and HR were taken once every three minutes. Once the client's HR and RPE measures were close to resting values, the treadmill was stopped. Final time, HR, blood pressure, and RPE were recorded. To calculate  $VO_{2peak}$ , the Bruce active and sedentary men and women generalized equations were used. If the subject was male, the following equation will be utilized:  $VO_{2peak} = 14.76 - 1.379 (\text{time}) + 0.451 (\text{time}^2) - 0.012 (\text{time}^3)$ .

If the participant was female, the following equation was used:  $VO_{2peak} = 4.38 (\text{time}) - 3.90$ .

Table 2

*The Bruce treadmill protocol*

Stage	Time	Speed	Grade	HR	BP	RPE	SpO <sub>2</sub>
<b>Warm -Up</b>	2-3 Min.	1.7	0%				
<b>1</b>	3 min.	1.7	10%				
<b>2</b>	3 min.	2.5	12%				
<b>3</b>	3 min.	3.4	14%				
<b>4</b>	3 min.	4.2	16%				
<b>5</b>	3 min.	5.0	18%				
<b>6</b>	3 min.	5.5	20%				
<b>7</b>	3 min.	6.0	22%				

**Rocky Mountain Cancer Rehabilitation Institute  
Protocol Gas Analysis**

Gas analysis has been deemed the gold standard and most accurate method in determining  $VO_{2peak}$  (Crouter, Antczak, Hudak, DellaValle, & Haas, 2006; Bassett Jr. et al., 2001). Handrail usage and the treadmill protocol that was used for GA was identical to the RMCRI protocol previously described. The metabolic equipment (ADInstruments,

Colorado Springs, CO.) was a 35 Series Data Acquisition System research grade metabolic cart, and has been used in over 30 years of research studies (Connolly & Hosking, 2005; Fatouleh & Macefield, 2011; Sealey, Leicht, Spinks, & Sinclair, 2010; Connolly, 2011; Guner et al., 2007; Matsui, Hattori, Takase, & Ishihara, 2006; Hirakawa, Oikawa, Bishop, & Hayashida, 2003; Liu, Li, Zeng, Zhong, & Chen, 2013). Before each test, the metabolic cart was calibrated. Oxygen ( $O_2$ ) and carbon dioxide ( $CO_2$ ) transducers were used. The carbon dioxide transducer was calibrated using two gas samples with known  $CO_2$  concentrations. The first was room air, which has a  $CO_2$  content of 0.03% (atmospheric  $CO_2$ ). The second gas had a  $CO_2$  content of 4.99%  $CO_2$ . The oxygen transducer was calibrated using two gases of known composition and with oxygen concentrations appropriate to the range of measurements that were expected. Room air was used for one of the gases. This has an  $O_2$  content of 21%. A second concentration of 12.01% was used to represent an intermediate  $O_2$  concentration. Balanced nitrogen was also used.

The flow head of the metabolic cart was utilized along with a spirometer flow head, which are precision differential pressure transducers for measuring variables such as inspiration and expiration flows. It measured differential pressure across fine gauze mounted in the flow head. The spirometer was calibrated to read in terms of flow (L/s), which was accomplished by injecting a known volume of air through the breathing circuit and integrating the flow signal in LabChart. A 3-liter MLA5530 calibration syringe was used for this purpose and simulated a single expiration. The plunger of the syringe was depressed at a steady rate, neither too quickly nor too slowly, and the plunger did not come to an abrupt stop at the end of the syringe.

Before the test began, each subject received a detailed explanation as to how and why the metabolic cart was being used. The respiration mask was then attached to the subject's face and held in place by Velcro straps. A tube was then connected to the respiration mask to the metabolic cart. Participants were instructed to try and breathe primarily through their mouths, not their noses. A total of four CES's were used for each metabolic cart test to ensure safety. One was responsible for changing the speed and grade of the protocol. A second recorded HR and RPE every minute, as well as termination time. The respiration mask made the participant inaudible, so they were instructed to give RPE using their fingers (ex. two fingers up = RPE of a two). A third stood behind the treadmill and be available for spotting purposes, and a final one set up and ran the metabolic cart during the test. Due to the metabolic cart, the CES was able to directly see what the subject's true  $\text{VO}_2$  was at any given moment. Additionally,  $\text{VO}_2$  was plotted on a graph in real-time to make the highest  $\text{VO}_2$  value easily distinguishable. Participants were encouraged to push themselves to what they perceived as their maximal effort. Termination criteria was identical to the RMCRI protocol. If any of these criterion were met, the subject entered a cool-down period. Heart rate and RPE were measured every minute until resting measures were achieved. Also, RER,  $\text{O}_2$ , and  $\text{CO}_2$  were recorded every ten seconds and when they returned to resting measures, the treadmill was deemed safe to stop.  $\text{VO}_{2\text{peak}}$  was determined by taking the highest  $\text{VO}_2$  value that was observed during the test. This value was recorded in liters per minute (L/min). To convert this to  $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , the following equation was used:  $[(\text{L}/\text{min} \times 1000)/\text{body weight (kg)}]$ . Additionally,  $\text{VO}_{2\text{peak}}$  was calculated via ACSM's walking and

running equations using the last completed stage during the GA test. This value was then compared to the value obtained via GA.

### **Pilot Study**

To assess the feasibility and tolerance to these protocols, a pilot study was performed in which ten CS completed all three protocols. These were CS who were participants in RMCRI's rehabilitation program. The tests and procedures were explained exactly as described above. These subjects completed all protocols over three weeks, with a week of rest following each completed test. A one week increment was chosen as this is the standard time allotted for recovery and rest between initial assessments and entry into the standard RMCRI program. Deconditioning was also unlikely during this time as subjects were continuing low-to-moderate exercise sessions in between each test. Initial HR, RPE, SpO<sub>2</sub>, BP, and body weight were recorded. Testing and termination criteria were identical to the procedures listed in the RMCRI protocol. Using the statistical analysis Friedman's test, no significant differences in VO<sub>2peak</sub> were observed between the BTP, GA, or RMCRI protocol ( $p = 0.19$ ). The mean VO<sub>2peak</sub> was  $26 \pm 7 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ; a moderate correlation was observed between the BTP and metabolic cart values ( $r = 0.63$ ), and a strong correlation was witnessed between GA and RMCRI VO<sub>2peak</sub> values ( $r = 0.93$ ). No adverse side effects were observed in any of the ten subjects after the completion of the tests. Additionally, because no differences were found in VO<sub>2peak</sub>, a training effect was not to be expected. Although the GA and BTP caused some discomfort, all protocols were tolerated. It should be noted that when all participants were asked which protocol they felt was the most appropriate given their current health, all ten preferred the RMCRI protocol.

### Statistical Analysis

A power analysis was run using the statistical program G-Power (version 3.1) prior to the start of the study to determine appropriate sample sizes. Effect sizes, which are descriptive statistics that convey the practical significance of results, were determined. Using the differences and the standard deviations between the observations, a medium effect size was used for the cancer survivor subjects with a level confidence of 95%. For the control participants, a large effect size with a level confidence of 95% was used due to a smaller sample size. For both groups, a repeated measures ANOVA was utilized to examine differences in  $VO_{2peak}$  values determined by RGAP, EVACSM,  $VO_{2peak}$  determined by generalized prediction  $VO_{2peak}$  equations following a BTP, and RWOGAP. Assumptions included 1) the dependent variable ( $VO_{2peak}$ ) was continuous, 2) the independent variable (treadmill protocols) were matched pairs, 3) there were no significant outliers in the related groups, and 4) the distribution of the dependent variable was approximately normally distributed. Post-hoc Tukey pair-wise comparisons were run on any statistical data requiring follow-up analyses. An unpaired t-test was utilized to examine differences between the AH in CS group in age, weight, RHR, RSBP, and RDBP.

A Pearson-r correlation was run to determine the strength of relationship for  $VO_{2peak}$  for both the cancer survivor group and the control group between RGAP and RWOGAP,  $VO_{2peak}$  from RGAP and EVACSM, and RGAP and generalized prediction  $VO_{2peak}$  equations via a BTP for the CS. Statistical analyses was performed using the Statistical Package for the Social Sciences software package (SPSS, Chicago, IL.).



Significance levels were set at  $p < 0.05$  and a Pearson correlation coefficient  $r > 0.80$  with GA was set to deem a protocol to be valid.

## **CHAPTER IV**

### **RESULTS**

The purpose of this study was to assess construct validity of the RMCRI multi-stage treadmill protocol for a cancer-specific population against standard metabolic gas analysis and the Bruce treadmill protocol.

#### **Participant Characteristics**

Table 3 displays cancer types of the CS. Tables 4 and 5 display gender and resting characteristics of all participants, respectively. The AH group was comprised of eight males and eight females, with a mean age of  $46 \pm 13$  years of age and mean weight of  $72 \pm 20.9$  kilograms (kg). The average resting heart rate (RHR), systolic blood pressure (RSBP), and diastolic blood pressure (RDBP) was  $79 \pm 15$  bpm,  $116 \pm 9$  mmHg, and  $77 \pm 9$  mmHg, respectively. There were no significant differences observed between RHR ( $p = 0.68$ ), RSBP ( $p = 0.21$ ), and RDBP ( $p = 0.45$ ) among the AH group. Of the AH subjects, 9 (56%) participants previously underwent surgery, but those surgeries were unrelated to cancer.

The CS group consisted of 36 females and nine males with a mean age of  $61.0 \pm 12$  years and a mean weight of  $75 \pm 14$  kg. RHR, RSBP, and RDBP were  $83 \pm 15$  bpm,  $122 \pm 13$  mmHg, and  $75 \pm 13$  mmHg, respectively. No significant differences were observed between RHR ( $p = 0.96$ ), RSBP ( $p = 0.30$ ), and RDBP ( $p = 0.39$ ) prior to the three individual tests. Of the CS, 12 participants (27%) underwent surgery only, two

participants (4%) underwent radiation only, six participants (13%) underwent surgery and radiation treatments, one participant (2%) underwent radiation and chemotherapy, nine participants (20%) underwent surgery and chemotherapy, and 15 participants (34%) underwent surgery, chemotherapy, and radiation. All participants completed each  $\text{VO}_{2\text{peak}}$  assessment without complications.

There were no significant differences observed in weight ( $p = 0.81$ ), RHR ( $p = 0.55$ ), RSBP ( $p = 0.06$ ), and RDBP ( $p = 0.87$ ) between the CS and AH groups. The CS group was significantly older than the AH group ( $61 \pm 12$  vs.  $48.6 \pm 14.1$ ;  $p = 0.006$ ).

Table 3

<i>Cancer Types</i>	
<b>Cancer Type</b>	<b>N</b>
Breast	21
Lymphoma/Leukemia	3
Prostate	3
Lung	3
Ovarian	2
Brain	2
Rectal	2
Skin	2
Uterine	2
Adenocarcinoma	2
Colon	1
Multiple Myeloma	1
Thyroid	1

Table 4

*Gender Characteristics*

	<b>Males</b>	<b>Females</b>
<b>Cancer Survivors</b>	9	36
<b>Control Subjects</b>	8	8
<b>Total</b>	17	44

Table 5

*Age, Weight, and Resting Characteristics*

	<b>Cancer Survivors</b>			<b>Control Subjects</b>			<b>P-Value</b>
<b>Age</b>	61	±	12	49	±	14	0.006
<b>Weight (kg)</b>	75	±	14	72	±	21	0.81
<b>RHR</b>	83	±	15	79	±	15	0.55
<b>RSBP</b>	122	±	13	116	±	9	0.06
<b>RDBP</b>	75	±	13	77	±	9	0.87

Note: bpm = beats per minute; mmHg = millimeters of mercury. Data are presented as mean ± SD.

Table 6

*Mean Peak Exercise Values*

	<i>RGAP</i>			<i>EVACSM</i>			<i>BTP</i>			<i>RWOGAP</i>			<b>P-Value</b>
<b>Cancer Survivors</b>													
HR	159.0	±	17.0		-		152.0	±	20.0	157.0	±	19.0	<0.05 <sup>δ†</sup>
SBP	150.0	±	14.0		-		150.0	±	14.0	152.0	±	13.0	0.31
DBP	76.0	±	19.0		-		78.0	±	9.0	79.0	±	8.0	0.76
RPE	9.0	±	1.0		-		9.0	±	1.0	9.0	±	1.0	0.2
RER	0.9	±	0.1		-								-
Treadmill time (min)	12.1	±	2.8		-		8.1	±	2.3	12.6	±	3.0	<0.05* <sup>δ†</sup>
VO <sub>2</sub> (mL•kg <sup>-1</sup> •min <sup>-1</sup> )	26.8	±	7.0	26.2	±	6.5	29.2	±	8.1	27.1	±	6.5	<0.05 <sup>δ†</sup>
VO <sub>2</sub> (L/min)	1.9	±	0.4	1.9	±	0.8	2.2	±	0.7	2.0	±	0.8	<0.05 <sup>δ†</sup>
VO <sub>2</sub> (METS)	7.6	±	2.0	7.4	±	2.2	8.3	±	2.3	7.7	±	1.8	<0.05 <sup>δ†</sup>
<b>Control Subjects</b>													
HR	171.0	±	16.0		-		174.0	±	16.0	177.0	±	12.0	0.673
SBP	152.0	±	18		-		155.0	±	23.0	152.0	±	13.0	0.846
DBP	81.0	±	8.0		-		78.0	±	12.0	82.0	±	10.0	0.451
RPE	9.0	±	1.0		-		9.0	±	1.0	9.0	±	1.0	0.204
RER	1.1	±	0.1		-								-
Treadmill time	16.4	±	3.8		-		10.6	±	2.7	16.6	±	3.6	<0.05 <sup>δ†</sup>
VO <sub>2</sub> (mL•kg <sup>-1</sup> •min <sup>-1</sup> )	38.3	±	16.7	38.3	±	8.4	39.8	±	10.6	38.7	±	7.3	0.724
VO <sub>2</sub> (L/min)	2.7	±	1.0	2.7	±	1.0	2.8	±	0.8	2.7	±	0.8	0.692
VO <sub>2</sub> (METS)	10.3	±	4.0	10.3	±	2.4	10.1	±	4.6	10.4	±	3.3	0.766

Note: HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; RPE = rating of perceived exertion; RER = respiratory exchange ratio; \* denotes a p value < 0.05 RGAP vs. RWOGAP, <sup>δ</sup> denotes a p value < 0.05 RGAP vs. BTP; <sup>†</sup> denotes a p value < 0.05 BTP vs. RWOGAP; - signifies same obtained value from RGAP.

### **Validity of Peak Volume of Oxygen Consumption Assessments for the Apparently Healthy Control Participants**

Table 6 depicts average peak treadmill variables. Criteria to be classified as a  $\text{VO}_{2\text{peak}}$  test were met 100% of the time. There were no significant differences between average peak HR ( $p = 0.67$ ), SBP ( $p = 0.85$ ), DBP ( $p = 0.45$ ), and RPE ( $p = 0.20$ ) values between any of the protocols. Figure 1 displays mean  $\text{VO}_{2\text{peak}}$  values ( $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) for the AH subjects. There were no significant differences in the average  $\text{VO}_{2\text{peak}}$  ( $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) between the RGAP ( $38.3 \pm 16.7$ ), EVACSM ( $38.3 \pm 8.4$ ), BTP ( $39.8 \pm 10.6$ ), or RWO GAP ( $38.7 \pm 7.3$ ) ( $p = 0.72$ ). No significant differences were observed in average  $\text{VO}_{2\text{peak}}$  (L/min) between RGAP ( $2.7 \pm 1.1$ ), EVACSM ( $2.7 \pm 0.8$ ), BTP ( $2.8 \pm 0.8$ ), or RWO GAP ( $2.7 \pm 0.8$ ) ( $p = 0.69$ ). There were no significant differences in average peak MET values between RMCRI gas analysis protocol ( $10.3 \pm 4.8$ ), estimated  $\text{VO}_{2\text{peak}}$  using the last completed stage of RGAP using ACSM's walking and running equations, ( $10.3 \pm 2.4$ ), BTP ( $10.1 \pm 4.6$ ), or Rocky Mountain Cancer Rehabilitation Institute without gas analysis protocol ( $10.4 \pm 3.3$ ) ( $p = 0.77$ ). Average total peak treadmill time observed was significantly greater during RGAP ( $16.4 \pm 3.8$  min) than BTP ( $10.6 \pm 2.7$  min) ( $p = 0.001$ ), and RWO GAP average treadmill time ( $16.69 \pm 3.66$  min) was significantly greater compared to total time on the BTP ( $p = 0.001$ ). Average peak RER was attainable only via GA, and was  $1.19 \pm 0.09$ .

### **Validity of Peak Volume of Oxygen Consumption Assessments for Cancer Survivors**

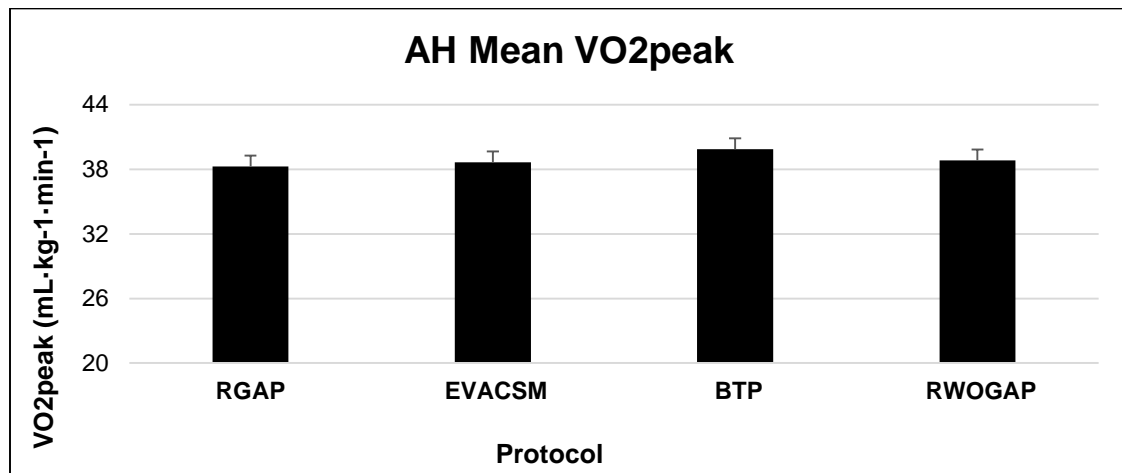
Table 6 depicts average peak treadmill variables. Criteria to be classified as a  $\text{VO}_{2\text{peak}}$  test were met 100% of the time. There were no significant differences in peak systolic blood pressure ( $p = 0.31$ ), diastolic blood pressure ( $p = 0.76$ ), or rating of

perceived exertion ( $p = 0.20$ ) values. Average peak HR was significantly lower in BTP ( $151.9 \pm 19.7$ ) when compared to both RGAP ( $158.9 \pm 16.7$ ) ( $p = 0.01$ ) and RWO GAP ( $156.9 \pm 19.1$ ) ( $p = 0.01$ ). Figure 2 displays mean  $\text{VO}_{2\text{peak}}$  values for CS.  $\text{VO}_{2\text{peak}}$  values were significantly lower for RGAP than the BTP ( $26.8 \pm 7.0$  vs.  $29.2 \pm 8.0$ , respectively) ( $p = 0.01$ ), significantly lower in RWO GAP compared to the BTP value ( $27.1 \pm 6.5$  vs.  $29.2 \pm 8.0$ , respectively) ( $p = 0.01$ ), and the EVACSM was significantly lower compared to BTP ( $26.2 \pm 6.5$  vs.  $29.2 \pm 8.0$ , respectively) ( $p = 0.01$ ). The Bruce treadmill protocol had significantly higher achieved METS compared to Rocky Mountain Cancer Rehabilitation Institute gas analysis protocol ( $8.3 \pm 2.3$  vs.  $7.6 \pm 2.0$ , respectively) ( $p = 0.03$ ), as well as significantly higher achieved METS compared to RWO GAP ( $8.3 \pm 2.3$  vs.  $7.7 \pm 1.8$ , respectively) ( $p = 0.03$ ).  $\text{VO}_{2\text{peak}}$  (L/min) was significantly greater in BTP compared to RGAP ( $2.20 \pm 0.78$  vs.  $1.9 \pm 0.4$ , respectively) ( $p = 0.009$ ), and significantly higher in the BTP compared to RWO GAP ( $2.20 \pm 0.78$  vs.  $2.0 \pm 0.8$ , respectively) ( $p = 0.009$ ). Total treadmill time was significantly higher on RGAP ( $12.1 \pm 2.8$ ) compared to total time on the BTP ( $8.1 \pm 2.3$ ) ( $p = 0.001$ ), significantly higher on RWO GAP compared to the BTP ( $12.6 \pm 3.0$  vs.  $8.1 \pm 2.3$ , respectively) ( $p = 0.001$ ), and significantly higher on RWO GAP compared to RGAP ( $12.6 \pm 3.0$  vs.  $12.1 \pm 2.8$ , respectively) ( $p = 0.01$ ). Average peak respiratory exchange ratio was attainable only via GA, and was  $0.9 \pm 0.1$ .

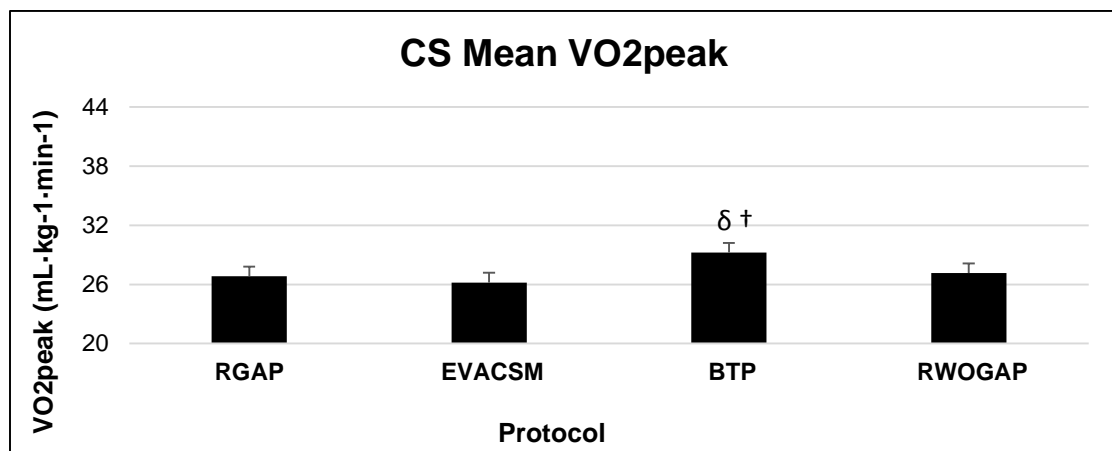
### Correlation Analyses

Figures 3-5 display correlations for the apparently healthy group. Positive strong correlations were observed between RGAP and EVACSM ( $r = 0.90$ ), the BTP and RPGA ( $r = 0.83$ ), and RGAP and RWO GAP ( $r = 0.92$ ). Correlations for the cancer survivor

group are seen in Figures 6-8. There were strong positive correlations observed between the  $\text{VO}_{2\text{peak}}$  obtained from RGAP and from EVACSM ( $r = 0.90$ ) and between  $\text{VO}_{2\text{peak}}$  from RGAP and RWO GAP ( $r = 0.81$ ). There was a moderate, positive correlation between RGAP  $\text{VO}_{2\text{peak}}$  and the BTP  $\text{VO}_{2\text{peak}}$  ( $r = 0.51$ ).



*Figure 1.* Mean  $\text{VO}_{2\text{peak}}$  values for Apparently Healthy Control Group. RGAP, RMCRI gas analysis protocol; EVACSM, estimated  $\text{VO}_{2\text{peak}}$  calculated from the last completed stage of the GA test using ACSM's walking/running equations; BTP, Bruce treadmill protocol; RWO GAP, RMCRI without gas analysis protocol. Data are mean  $\pm$  SD



*Figure 2.* Mean  $\text{VO}_{2\text{peak}}$  for Cancer Survivor Group. RGAP, RMCRI gas analysis protocol; EVACSM, estimated  $\text{VO}_{2\text{peak}}$  calculated from the last completed stage of the GA test using ACSM's walking/running equations; BTP, Bruce treadmill protocol; RWO GAP, RMCRI without gas analysis protocol. <sup>†</sup> $p < 0.05$  RGAP vs. Bruce value; <sup>δ</sup> $p < 0.05$  Bruce value vs. RGAP. Data are means  $\pm$  SD.



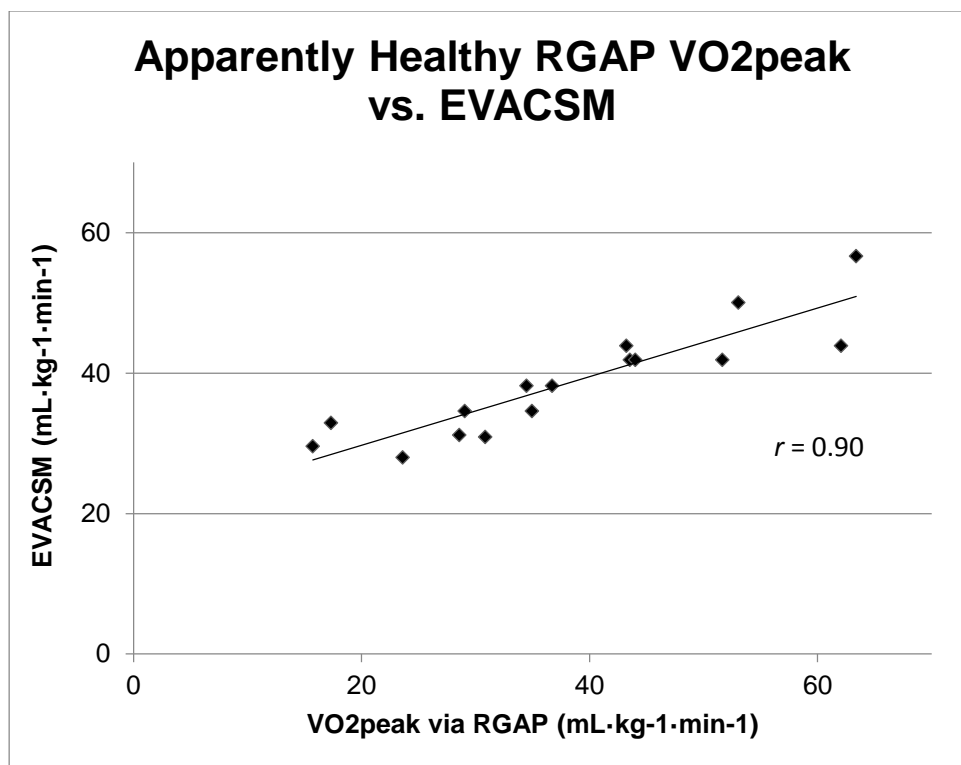


Figure 3. AH correlation between RGAP VO<sub>2</sub>peak and EVACSM

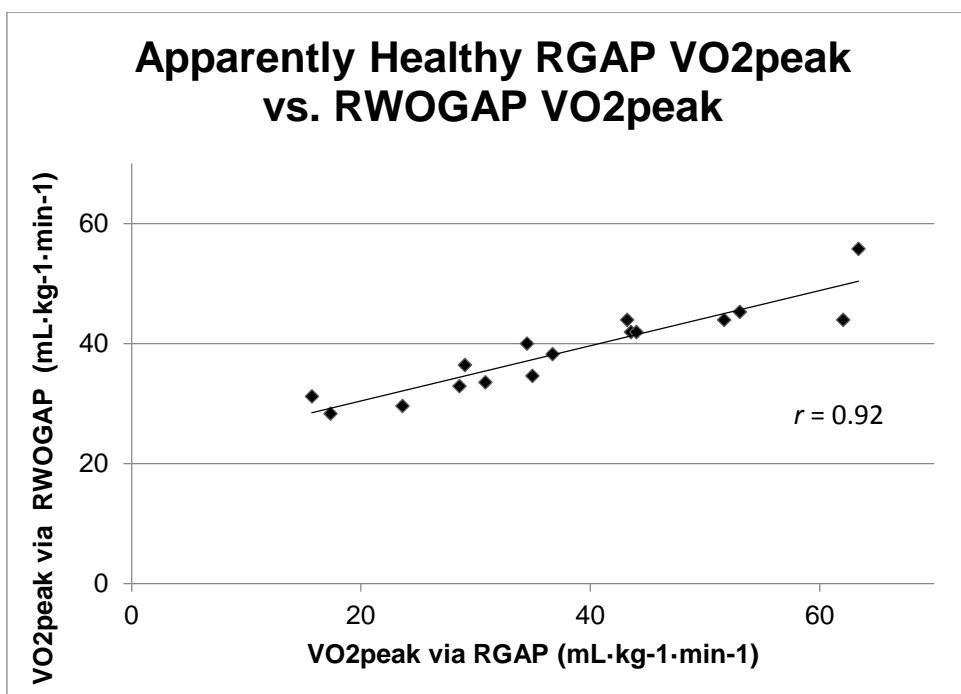


Figure 4. AH correlation between RGAP VO<sub>2</sub>peak and RWO GAP VO<sub>2</sub>peak

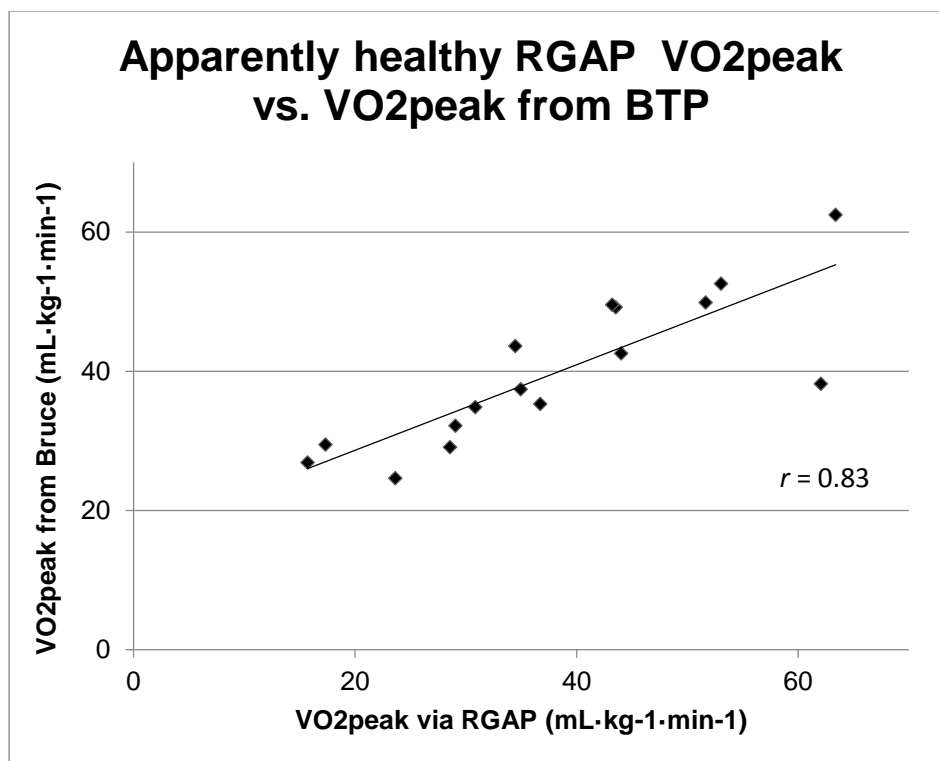


Figure 5. AH correlation between RGAP VO<sub>2</sub>peak and Bruce VO<sub>2</sub>peak Protocol

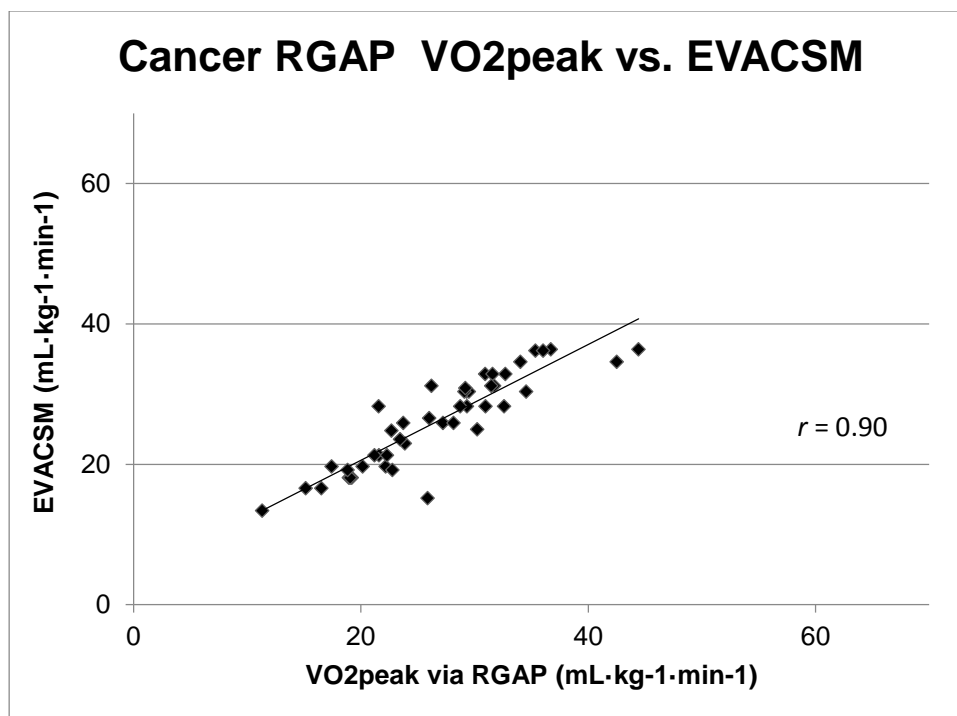


Figure 6. CS correlation between RGAP VO<sub>2</sub>peak and EVACSM

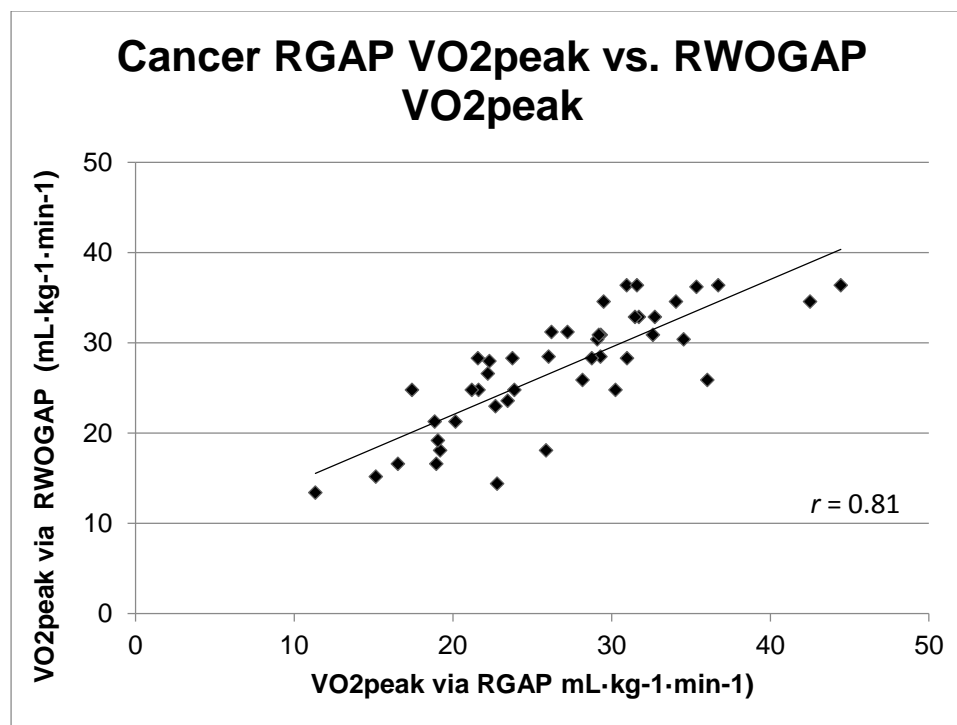


Figure 7. CS correlation between RGAP VO<sub>2</sub>peak and RWOGAP VO<sub>2</sub>peak

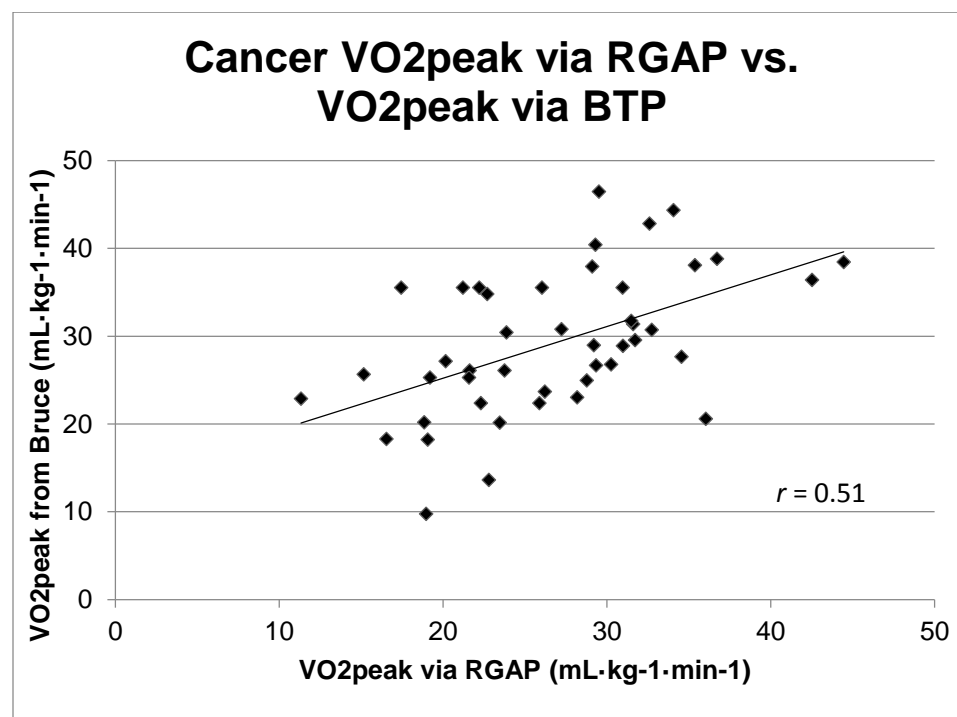


Figure 8. CS correlation between RGAP VO<sub>2</sub>peak and Bruce VO<sub>2</sub>peak Protocol

The statistical analysis repeated measures ANOVA test was confirmed to be an appropriate test to compare  $VO_{2peak}$  values. The dependent variable ( $VO_{2peak}$ ) was a continuous value, the independent variables (RGAP, BTP, and RWO GAP) were all matched pairs, and there were no significant outliers in the related groups. Additionally, the  $VO_{2peak}$  values were plotted on a histogram to illustrate the distribution of all  $VO_{2peak}$  points. From this histogram, the dependent variable appeared to be approximately normally distributed. Due to all assumptions being met, along with the normal distribution of the data, the repeated measures ANOVA was the appropriate statistical test for this data.

## **CHAPTER V**

### **MANUSCRIPT**

#### **Introduction**

Today there are approximately 13.7 million Americans living with a history of cancer, and over 1.6 million new diagnoses of cancer are expected this year (ACS, 2015). This year, more than half a million of Americans are expected to succumb to this disease, as it is the second leading cause of death (ACS, 2015). Fortunately, due to recent advancements in cancer treatments and diagnoses, the 5-year survival rate for cancer is now at 68%. The increased survival rate may, consequently, result in many cancer survivors suffering from deleterious side effects of cancer and cancer treatments. Due to these side effects, cancer rehabilitation programs are being implemented to combat these symptoms through prescriptive exercise interventions. The goal of these programs is to improve cancer survivors' functional capacity as well as their psychosocial well-being (Schmitz et al., 2010).

It has been demonstrated that physical activity performed before, during, and after cancer treatment plays an instrumental role in improving physiological and psychological factors, such as increased maximal oxygen consumption ( $VO_{2max}$ ) and quality of life (QOL) (Anderson et al., 2010; Groeneveldt et al., 2013).  $VO_{2max}$  is considered the best indicator of overall health and is most accurately obtained via a metabolic cart utilizing gas analysis (GA). Greater  $VO_{2max}$  values have been associated with reduced all-cause

cancer mortality (Gulati et al., 2003; Myers et al., 2002; Sawada et al., 2003). This stresses the importance of establishing an accurate  $\text{VO}_{2\text{max}}$  for cancer survivors when designing a rehabilitative exercise intervention. Although  $\text{VO}_{2\text{max}}$  is considered to be the best measure of aerobic capacity,  $\text{VO}_{2\text{peak}}$  is often used with special populations due to the inability of achieving  $\text{VO}_{2\text{max}}$  criteria and has been shown to be as accurate  $\text{VO}_{2\text{max}}$  (Day et al., 2003; Howley, 2007; Jones et al., 2011; Kim et al., 2006).

Graded exercise tests are normally performed by cancer survivors to determine  $\text{VO}_{2\text{peak}}$  and exercise capacity, allowing clinicians to form a more accurate prescription of exercise for rehabilitation. Treadmill running/walking and cycle ergometry are the most commonly used modalities for  $\text{VO}_2$  tests, but treadmill protocols have been reported to elicit higher and more accurate  $\text{VO}_{2\text{peak}}$  values than cycle ergometry protocols (Moody et al., 1969; Pollock et al., 1982; Astrand & Rodahl, 1977). The Bruce treadmill protocol (BTP), which is used by more than half of the clinicians in North America (Chugh, 2012; Hill & Timmis, 2002; Marinov et al., 2002; Stuart & Ellestad, 1980), is highly correlated with  $\text{VO}_{2\text{peak}}$  and is considered to be one of the most accurate predictors of cardiorespiratory fitness. This protocol however, elicits increased workload via large increases in speed and incline with each stage, which may result in inaccurate  $\text{VO}_{2\text{peak}}$  values (Cunha et al., 2012; Foster et al., 1984; Lee et al., 2011; Redwood, Rosing, Goldstein, & Epstein, 1971; Sullivan & McKirnan, 1984;). Furthermore, protocols that have large single-stage increases in exercise intensity may be unsuitable for cancer survivors and may result in inaccurate measurements of  $\text{VO}_{2\text{peak}}$ .

Currently a cancer-specific treadmill protocol does not exist. To address this issue, the Rocky Mountain Cancer Rehabilitation Institute (RMCRI) developed the

RMCRI multi-stage treadmill protocol for the measurement of  $\text{VO}_{2\text{peak}}$  in the cancer population. This protocol is designed to increase speed and grade in minimal increments with shorter stages providing a more gradual increase in intensity. This slowed progression of intensity may be perceived as less intimidating for cancer survivors, unlike the sudden, large increases in intensity with the BTP (Bader, Maguire, & Balady, 1999; Will & Walter, 1999). Specifically, cancer survivors who are suffering from cancer and cancer-related toxicities may be better able to tolerate the lower intensities associated with the RMCRI protocol, allowing the patients to exercise longer, thereby establishing a more accurate  $\text{VO}_{2\text{peak}}$  value. This allows Cancer Exercise Specialists (CES) the ability to form an accurate prescription of exercise and a subsequent exercise intervention.

With the increase in survival rates, cancer rehabilitation programs are serving an integral role in assisting patients in recovery and regaining health. Establishing an accurate  $\text{VO}_{2\text{peak}}$  value and baseline measure of cardiorespiratory endurance is the first and foremost step in this process. This demonstrates the need to validate the effectiveness of a cancer-specific protocol. Therefore, the purpose of this study was to assess the construct validity of the RMCRI multi-stage treadmill protocol in a cancer-specific population against standard metabolic GA and the standard BTP.

## **Methods**

### **Subjects**

Participants were enrolled in the study upon completion of a medical history form and after signing an informed consent approved by the University of Northern Colorado's Institutional Review Board (Appendix D). A total of 61 subjects participated. Participants who were cancer survivors (CS) ( $n = 45$ ) were enrolled in the Rocky

Mountain Cancer Rehabilitation Institute's (RMCRI) cancer rehabilitation program.

Apparently healthy (AH) control subjects ( $n = 16$ ) were recruited from the University of Northern Colorado (UNC) campus through recruitment fliers distributed via email.

Participants were excluded if they had a history of congestive heart failure, a history of myocardial infarction, chronic lung disease, asthma, significant ambulatory issues, history of coughing up blood, a history of fainting, epilepsy, and/or neuropathy in the lower extremities.

### **Experimental Design**

Participants who qualified for the study completed three separate treadmill protocols over the course of three weeks. The order of completion was determined by random assignment using the Statistical Analysis System (SAS) PROC PLAN randomization procedure (SAS, 9.3). A week of rest following each treadmill test was given to allow subjects to recover and reduce the risk of fatigue. The following protocols were performed: RMCRI  $\text{VO}_{2\text{peak}}$  gas analysis protocol (RGAP),  $\text{VO}_{2\text{peak}}$  Bruce treadmill protocol (BTP), and RMCRI  $\text{VO}_{2\text{peak}}$  without GA protocol (RWO GAP). Resting blood pressure (BP), heart rate (HR), and blood oxygen saturation ( $\text{SpO}_2$ ) were measured before all tests, along with the subject's body weight. BP was determined using manual auscultation via a blood pressure cuff and stethoscope, heart rate was determined using a Polar<sup>®</sup> heart rate monitor, and  $\text{SpO}_2$  was determined using a Clinical Guard<sup>®</sup> pulse oximeter. During all tests,  $\text{SpO}_2$  and HR were recorded once every minute, and rating of perceived exertion (RPE) and BP were recorded every three minutes. Depending upon the protocol, three to four Cancer Exercise Specialists (CES) conducted all treadmill tests to ensure subject safety. One CES was responsible for changing the grade and speed of



the treadmill and recording all information during the test, a second measured BP, a third stood behind the treadmill to spot the subject, and a fourth set up and operated a metabolic cart, when necessary.

For all tests, subjects were encouraged to refrain from using the handrails during the test, but if it was deemed necessary due to subject discomfort or increased risk, they held onto the handrails. The tests terminated when the participant felt they reached their maximum threshold of exertion on the treadmill and could not continue any further. The tests would also conclude if any of the following criteria were met: HR did not increase with increased intensity, systolic blood pressure (SBP) did not increase with intensity, DBP oscillated more than 10 mmHg from resting measure, SpO<sub>2</sub> dropped below 80%, and/or verbal consent of the participant to end the test due to any safety issues. A cool down period was conducted after completion of the test to ensure that the subject returned to their near resting vital measures. Final HR, BP, SpO<sub>2</sub>, and treadmill time were recorded.

Before each test begins, the participants will be given the following instructions:

1) one CES will be taking your blood pressure once every three minutes, 2) another CES will be recording all data from the test, as well as changing the speed and grades of the treadmill, 3) a pulse oximeter will be placed on your index finger, in which we will record your oxygen saturation at the end of every minute, 4) another CES 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's necessary, 7)

regardless 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 lower your vitals close to resting measures.

A test was deemed a  $VO_{2peak}$  test if at least two of the following criteria were met:

1) subject terminated test due to perceived maximal effort and fatigue, 2) heart rate was elevated to within ten beats per minute of the individual's estimated heart rate max, and 3) if a subject gave a RPE value on the modified Borg RPE scale of at least an eight. If at least two of these criteria were not met, the test results were not used. Four different values were compared using a repeated measures ANOVA test: 1)  $VO_{2peak}$  obtained from RGAP, 2) estimated  $VO_{2peak}$  from the last completed stage of the GA test using ACSM's walking/running equations (EVACSM), 3)  $VO_{2peak}$  peak from a peak BTP, and (4)  $VO_{2peak}$  calculated from RWO GAP.  $VO_{2peak}$  values from the RGAP test were compared with EVACSM to determine whether the ACSM equations were valid in determining  $VO_{2peak}$ . Values from BTP and RGAP were compared to determine whether BTP yields accurate values for cancer survivors. Finally, the RGAP values were compared to the values from RWO GAP to determine whether the metabolic cart may alter a cancer survivor's performance on a treadmill test.

### **Rocky Mountain Cancer Rehabilitation Institute Protocol**

This protocol consisted of 21 stages, with each being only one minute long. Speed and/or grade were increased at the completion of each stage. Details of this protocol are presented in Table 7. Participants were informed that they would be

performing a RMCRI  $\text{VO}_{2\text{peak}}$  treadmill test and that they could end the test whenever they deemed necessary, but were encouraged to continue as far as physically possible.

ACSM walking and running equations were used to calculate  $\text{VO}_{2\text{peak}}$  by using the last completed stage of the protocol. The subject determined whether he or she needed to walk or run at the last completed stage. If the subject was walking when the test was terminated, the following equation was used:  $\text{VO}_{2\text{peak}} = (0.1 \times S) + (1.8 \times S \times G) + 3.5$ ; where  $S$  = speed and  $G$  = grade. If a subject was holding onto the handrails and walking at the termination of the test, the following correction equation was used:  $\text{VO}_{2\text{peak}} = 0.694 [(0.1 \times S) + (1.8 \times S \times G) + 3.5] + 3.33$ . If the subject was running when the test was terminated, the following equation was used:  $\text{VO}_{2\text{peak}} = (0.2 \times S) + (0.9 \times S \times G) + 3.5$ . If the subject was running at the end of the test while holding on to the handrails the following correction equation was used:  $\text{VO}_{2\text{peak}} = 0.694 [(0.2 \times S) + (0.9 \times S \times G) + 3.5] + 3.33$  (American College of Sports Medicine, 2013).

Table 7

*Rocky Mountain Cancer Rehabilitation  
Institute Protocol*

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%	***

## **Bruce Protocol**

This protocol consists of seven stages which increase speed and grade in three minute increments. To calculate  $\text{VO}_{2\text{peak}}$ , the Bruce active and sedentary men and women generalized equations were used. If the subject was male, the following equation was utilized:  $\text{VO}_{2\text{peak}} = 14.76 - 1.379 (\text{time}) + 0.451 (\text{time}^2) - 0.012 (\text{time}^3)$ . If the participant used handrails, the following equation was used:  $\text{VO}_{2\text{peak}} = 0.694 [14.76 - 1.379 (\text{time}) + 0.451 (\text{time}^2) - 0.012 (\text{time}^3)] + 3.33$ . If the participant was female, the following equation was used:  $\text{VO}_{2\text{peak}} = 4.38 (\text{time}) - 3.90$ . If the participant used handrails, the following equation was used:  $\text{VO}_{2\text{peak}} = 0.694 [4.38 (\text{time}) - 3.90] + 3.33$ .

## **Rocky Mountain Cancer Rehabilitation Institute Gas Analysis**

Using a 35 Series Data Acquisition System research grade metabolic cart (ADInstruments, Colorado Springs, CO), expired gases were continuously collected where  $\text{VO}_2$  and  $\text{VCO}_2$  were recorded once every 10 seconds. Calibration of the metabolic cart was performed before each test with a 3 L syringe and precision gas mixtures. Before the test began, each subject received a detailed explanation as to how the test was conducted, and why the metabolic cart was being used. A respiration mask was attached to the subject's face and held in place by Velcro® straps. A tube connected the respiration mask to the metabolic cart. Participants were instructed to breathe primarily through their mouths, not their noses. The respiration mask made the participant inaudible, so participants were instructed to give RPE using their fingers (for example, two fingers up = RPE of two). In addition to standard termination criteria, this protocol ended if their  $\text{VO}_2$  reached a plateau or if their respiratory exchange ratio exceeded 1.15.

If any of these criteria were met, the test was terminated and the subject began a cool-down period.  $\text{VO}_{2\text{peak}}$  was determined by taking the highest  $\text{VO}_2$  value that was observed during the test and was recorded in liters per minute (L/min). To convert this to  $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , the following equation was used:  $[(\text{L}/\text{min} \times 1000)/\text{body weight (kg)}]$ .

Additionally,  $\text{VO}_{2\text{peak}}$  was calculated via ACSM's walking and running equations using the last completed stage during the GA test. This value was then compared to the value obtained via GA.

### **Statistical Analysis**

All data are presented as mean  $\pm$  standard deviation (SD). For the CS and AH group, a repeated measures ANOVA test was utilized to examine differences in  $\text{VO}_{2\text{peak}}$  values via a RGAP, EVACSM, generalized prediction  $\text{VO}_{2\text{peak}}$  equations following a BTP, and RWOGA. Independent sample t-tests were conducted to determine any differences between the CS and AH group in age, weight, and resting vitals. Post-hoc Tukey pair-wise comparisons were conducted on any statistical data requiring follow-up analyses.

A Pearson r correlation was conducted to examine the strength of relationship in  $\text{VO}_{2\text{peak}}$  for both the CS and AH group between RGAP and RWOGA,  $\text{VO}_{2\text{peak}}$  calculated from RGAP and EVACSM, and RGAP and generalized prediction  $\text{VO}_{2\text{peak}}$  equations via a BTP for the cancer survivors. Statistical analyses were performed using the Statistical Package for the Social Sciences software package (SPSS, Chicago, IL.). Significance levels were set at  $p \leq 0.05$  and a Pearson correlation coefficient  $r > 0.80$  with GA will be set to deem a protocol to be valid.

## Results

### Participant Characteristics

Table 8 displays cancer types of the CS. Tables 9 and 10 display gender and resting characteristics of all participants, respectively. The AH group was comprised of eight males and eight females, with a mean age of  $46 \pm 13$  years of age and mean weight of  $72 \pm 20.9$  kilograms (kg). The average resting heart rate (RHR), systolic blood pressure (RSBP), and diastolic blood pressure (RDBP) was  $79 \pm 15$  bpm,  $116 \pm 9$  mmHg, and  $77 \pm 9$  mmHg, respectively. There were no significant differences observed between RHR ( $p = 0.68$ ), RSBP ( $p = 0.21$ ), and RDBP ( $p = 0.45$ ) among the apparently healthy group. Of the AH subjects, 9 (56%) participants previously underwent surgery, but those surgeries were unrelated to cancer.

The cancer survivor group consisted of 36 females and nine males with a mean age of  $61.0 \pm 12$  years and a mean weight of  $75 \pm 14$  kg. Resting heart rate, resting systolic blood pressure, and resting diastolic blood pressure were  $83 \pm 15$  bpm,  $122 \pm 13$  mmHg, and  $75 \pm 13$  mmHg, respectively. No significant differences were observed between RHR ( $p = 0.96$ ), RSBP ( $p = 0.30$ ), and RDBP ( $p = 0.39$ ) prior to the three individual tests. Of the CS, 12 participants (27%) underwent surgery only, two participants (4%) underwent radiation only, six participants (13%) underwent surgery and radiation treatments, one participant (2%) underwent radiation and chemotherapy, nine participants (20%) underwent surgery and chemotherapy, and 15 participants (34%) underwent surgery, chemotherapy, and radiation. All participants completed each  $\text{VO}_{2\text{peak}}$  assessment without complications.

There were no significant differences observed in weight ( $p = 0.81$ ), resting heart rate ( $p = 0.55$ ), resting systolic blood pressure ( $p = 0.06$ ), and resting diastolic blood pressure ( $p = 0.87$ ) between the CS and AH groups. The CS group was significantly older than the AH group ( $61 \pm 12$  vs.  $48.6 \pm 14.1$ ;  $p = 0.006$ ).

Table 8

*Cancer Types*

<b>Cancer Type</b>	<b>N</b>
Breast	21
Lymphoma/Leukemia	3
Prostate	3
Lung	3
Ovarian	2
Brain	2
Rectal	2
Skin	2
Uterine	2
Adenocarcinoma	2
Colon	1
Multiple Myeloma	1
Thyroid	1



Table 9

*Gender Characteristics*

	<b>Males</b>	<b>Females</b>
<b>Cancer Survivors</b>	9	36
<b>Control Subjects</b>	8	8
<b>Total</b>	17	44

Table 10

*Age, Weight, and Resting Characteristics*

	<b>Cancer Survivors</b>			<b>Control Subjects</b>			<b>P-Value</b>
<b>Age</b>	61	±	12	49	±	14	0.006
<b>Weight (kg)</b>	74	±	14	72	±	21	0.81
<b>RHR</b>	83	±	15	79	±	15	0.55
<b>RSBP</b>	122	±	13	116	±	9	0.06
<b>RDBP</b>	75	±	13	77	±	9	0.87

Note: bpm = beats per minute; mmHg = millimeters of mercury. Data are presented as mean ± SD.

Table 11

*Mean Peak Exercise Values*

	<i>RGAP</i>			<i>EVACSM</i>			<i>BTP</i>			<i>RWOGAP</i>			<b>P-Value</b>
<b>Cancer Survivors</b>													
HR	159.0	±	17.0		-		152.0	±	20.0	157.0	±	19.0	<0.05 <sup>δ†</sup>
SBP	150.0	±	14.0		-		150.0	±	14.0	152.0	±	13.0	0.31
DBP	76.0	±	19.0		-		78.0	±	9.0	79.0	±	8.0	0.76
RPE	9.0	±	1.0		-		9.0	±	1.0	9.0	±	1.0	0.2
RER	0.9	±	0.1		-								-
Treadmill time (min)	12.1	±	2.8		-		8.1	±	2.3	12.6	±	3.0	<0.05* <sup>δ†</sup>
VO <sub>2</sub> (mL•kg-1•min-1)	26.8	±	7.0	26.2	±	6.5	29.2	±	8.1	27.1	±	6.5	<0.05 <sup>δ†</sup>
VO <sub>2</sub> (L/min)	1.9	±	0.4	1.9	±	0.8	2.2	±	0.7	2.0	±	0.8	<0.05 <sup>δ†</sup>
VO <sub>2</sub> (METS)	7.6	±	2.0	7.4	±	2.2	8.3	±	2.3	7.7	±	1.8	<0.05 <sup>δ†</sup>
<b>Control Subjects</b>													
HR	171.0	±	16.0		-		174.0	±	16.0	177.0	±	12.0	0.673
SBP	152.0	±	18		-		155.0	±	23.0	152.0	±	13.0	0.846
DBP	81.0	±	8.0		-		78.0	±	12.0	82.0	±	10.0	0.451
RPE	9.0	±	1.0		-		9.0	±	1.0	9.0	±	1.0	0.204
RER	1.1	±	0.1		-								-
Treadmill time	16.4	±	3.8		-		10.6	±	2.7	16.6	±	3.6	<0.05 <sup>δ†</sup>
VO <sub>2</sub> (mL•kg-1•min-1)	38.3	±	16.7	38.3	±	8.4	39.8	±	10.6	38.7	±	7.3	0.724
VO <sub>2</sub> (L/min)	2.7	±	1.0	2.7	±	1.0	2.8	±	0.8	2.7	±	0.8	0.692
VO <sub>2</sub> (METS)	10.3	±	4.0	10.3	±	2.4	10.1	±	4.6	10.4	±	3.3	0.766

Note: HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; RPE = rating of perceived exertion, RER = respiratory exchange ratio; \* denotes a p value < 0.05 RGAP vs. RWOGAP, <sup>δ</sup> denotes a p value < 0.05 RGAP vs. BTP; <sup>†</sup> denotes a p value < 0.05 BTP vs. RWOGAP; - signifies same obtained value from RGAP

### **Validity of Peak Oxygen Consumption Assessments for the Apparently Healthy Control Participants**

Table 11 depicts average peak treadmill variables. Criteria to be classified as a  $\text{VO}_{2\text{peak}}$  test were met 100% of the time. There were no significant differences between average peak HR ( $p = 0.67$ ), SBP ( $p = 0.85$ ), DBP ( $p = 0.45$ ), and RPE ( $p = 0.20$ ) values between any of the protocols. Figure 9 displays mean  $\text{VO}_{2\text{peak}}$  values ( $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) for the AH subjects. There were no significant differences in the average  $\text{VO}_{2\text{peak}}$  ( $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) between the RGAP ( $38.3 \pm 16.7$ ), EVACSM ( $38.3 \pm 8.4$ ), BTP ( $39.8 \pm 10.6$ ), or RWOOGAP ( $38.7 \pm 7.3$ ) ( $p = 0.72$ ). No significant differences were observed in average  $\text{VO}_{2\text{peak}}$  ( $\text{L}/\text{min}$ ) between RGAP ( $2.7 \pm 1.1$ ), EVACSM ( $2.7 \pm 0.8$ ), BTP ( $2.8 \pm 0.8$ ), or RWOOGAP ( $2.7 \pm 0.8$ ) ( $p = 0.69$ ). There were no significant differences in average peak MET values between Rocky Mountain Cancer Rehabilitation Institute Gas Analysis Protocol ( $10.3 \pm 4.8$ ), estimated  $\text{VO}_{2\text{peak}}$  from last completed stage of RMCRI gas analysis protocol ( $10.3 \pm 2.4$ ), Bruce treadmill protocol ( $10.1 \pm 4.6$ ), or RMCRI without gas analysis protocol ( $10.4 \pm 3.3$ ) ( $p = 0.77$ ). Average total peak treadmill time observed was significantly greater during RGAP ( $16.4 \pm 3.8$  min) than BTP ( $10.6 \pm 2.7$  min) ( $p = 0.001$ ), and RWOOGAP average treadmill time ( $16.69 \pm 3.66$  min) was significantly greater compared to total time on the BTP ( $p = 0.001$ ). Average peak RER was attainable only via GA, and was  $1.19 \pm 0.09$ .

### **Validity of Peak Oxygen Consumption Assessments for Cancer Survivors**

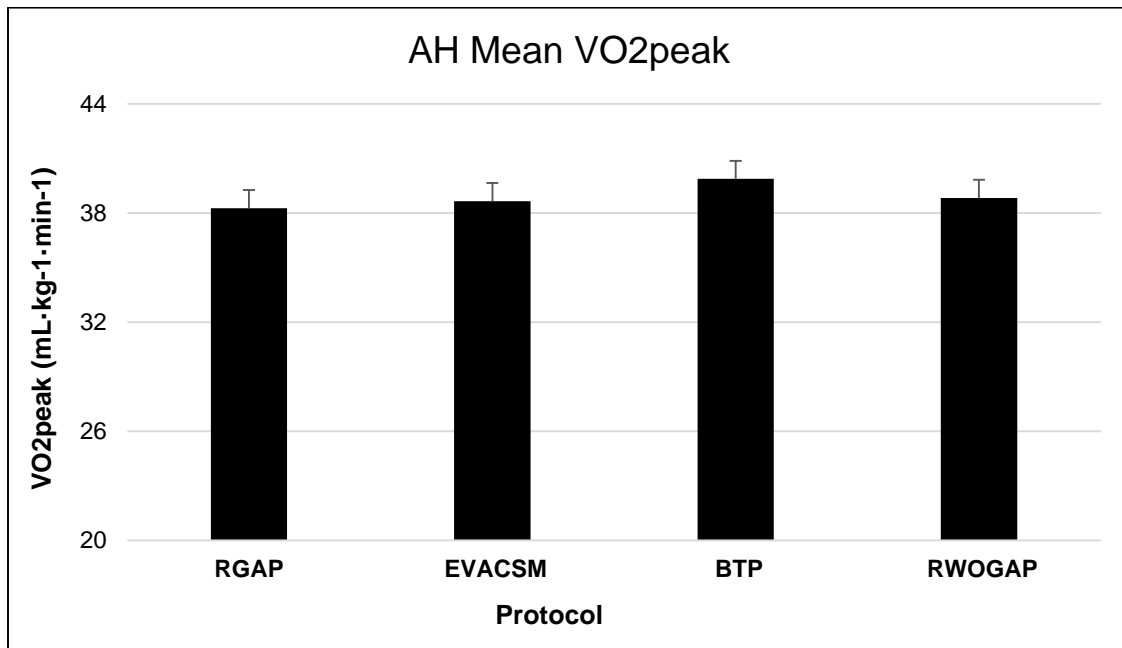
Table 11 depicts average peak treadmill variables. Criteria to be classified as a  $\text{VO}_{2\text{peak}}$  test were met 100% of the time. There were no significant differences in peak systolic blood pressure ( $p = 0.31$ ), diastolic blood pressure ( $p = 0.76$ ), or rating of

perceived exertion ( $p = 0.20$ ) values. Average peak HR was significantly lower in BTP ( $151.9 \pm 19.7$ ) when compared to both RGAP ( $158.9 \pm 16.7$ ) ( $p = 0.01$ ) and RWOOGAP ( $156.9 \pm 19.1$ ) ( $p = 0.01$ ). Figure 10 displays mean  $\text{VO}_{2\text{peak}}$  values for the cancer survivors.  $\text{VO}_{2\text{peak}}$  values were significantly lower for RMCRI gas analysis protocol than the Bruce treadmill protocol ( $26.8 \pm 7.0$  vs.  $29.2 \pm 8.0$ , respectively) ( $p = 0.01$ ), significantly lower in RWOOGAP compared to the BTP value ( $27.1 \pm 6.5$  vs.  $29.2 \pm 8.0$ , respectively) ( $p = 0.01$ ), and the EVACSM was significantly lower compared to BTP ( $26.2 \pm 6.5$  vs.  $29.2 \pm 8.0$ , respectively) ( $p = 0.01$ ). The Bruce treadmill protocol had significantly higher achieved METS compared to RGAP ( $8.3 \pm 2.3$  vs.  $7.6 \pm 2.0$ , respectively) ( $p = 0.03$ ), as well as significantly higher achieved METS compared to RMCRI without gas analysis protocol ( $8.3 \pm 2.3$  vs.  $7.7 \pm 1.8$ , respectively) ( $p = 0.03$ ).  $\text{VO}_{2\text{peak}}$  (L/min) was significantly greater in the Bruce treadmill protocol compared to RMCRI gas analysis protocol ( $2.20 \pm 0.78$  vs.  $1.9 \pm 0.4$ , respectively) ( $p = 0.009$ ), and significantly higher in the Bruce treadmill protocol compared to RMCRI without gas analysis protocol ( $2.20 \pm 0.78$  vs.  $2.0 \pm 0.8$ , respectively) ( $p = 0.009$ ). Total treadmill time was significantly higher on RGAP ( $12.1 \pm 2.8$ ) compared to total time on the BTP ( $8.1 \pm 2.3$ ) ( $p = 0.001$ ), significantly higher on RWOOGAP compared to the BTP ( $12.6 \pm 3.0$  vs.  $8.1 \pm 2.3$ , respectively) ( $p = 0.001$ ), and significantly higher on RWOOGAP compared to RGAP ( $12.6 \pm 3.0$  vs.  $12.1 \pm 2.8$ , respectively) ( $p = 0.01$ ). Average peak respiratory exchange ratio was attainable only via GA, and was  $0.9 \pm 0.1$ .

### **Correlation Analyses**

Figures 11-13 display correlations for the apparently healthy group. Positive strong correlations were observed between RGAP and EVACSM ( $r = 0.90$ ), the BTP and

RPGA ( $r = 0.83$ ), and RGAP and RWOOGAP ( $r = 0.92$ ). Correlations for the cancer survivor group are seen in Figures 14-16. There were strong positive correlations observed between the  $VO_{2peak}$  obtained from RGAP and from EVACSM ( $r = 0.90$ ) and between  $VO_{2peak}$  from RGAP and RWOOGAP ( $r = 0.81$ ). There was a moderate, positive correlation between RMCRI gas analysis protocol  $VO_{2peak}$  and the Bruce treadmill protocol  $VO_{2peak}$  ( $r = 0.51$ ).



*Figure 9.* Mean  $VO_{2peak}$  values for Apparently Healthy Control Group. RGAP, RMCRI gas analysis protocol; EVACSM, estimated  $VO_{2peak}$  calculated from the last completed stage of the GA test using ACSM's walking/running equations; BTP, Bruce treadmill protocol; RWOOGAP, RMCRI without gas analysis protocol. Data are mean  $\pm$  SD

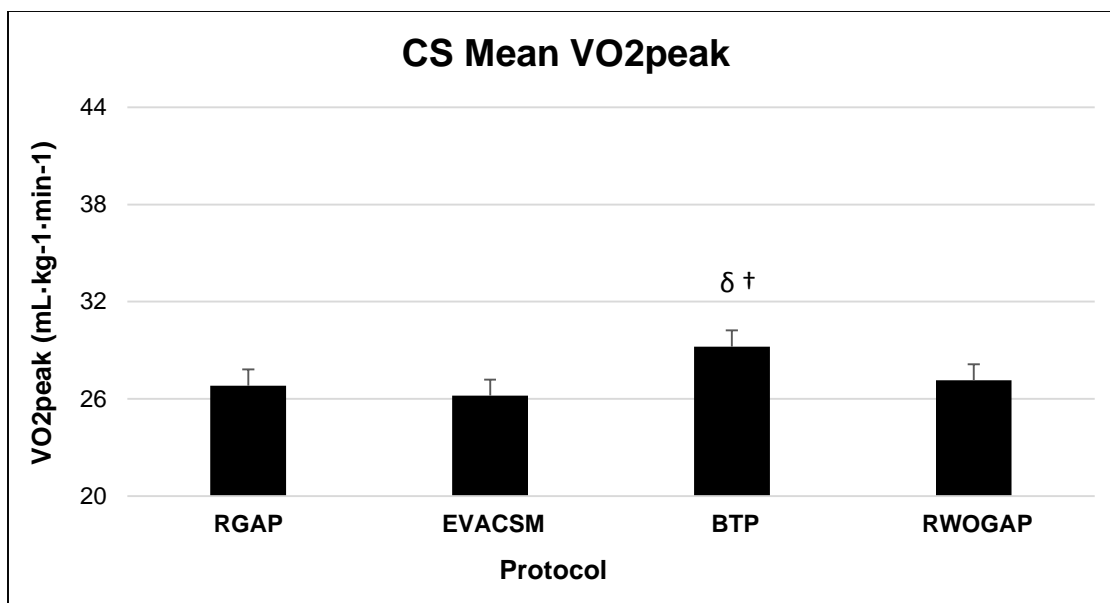


Figure 10. Mean VO<sub>2</sub>peaks for Cancer Survivor Group. RGAP, RMCRI gas analysis protocol; EVACSM, estimated VO<sub>2</sub>peak calculated from the last completed stage of the GA test using ACSM's walking/running equations; BTP, Bruce treadmill protocol; RWO GAP, RMCRI without gas analysis protocol. <sup>†</sup> $p < 0.05$  RGAP vs. Bruce value; <sup>δ</sup> $p < 0.05$  Bruce value vs. RGAP. Data are means  $\pm$  SD.

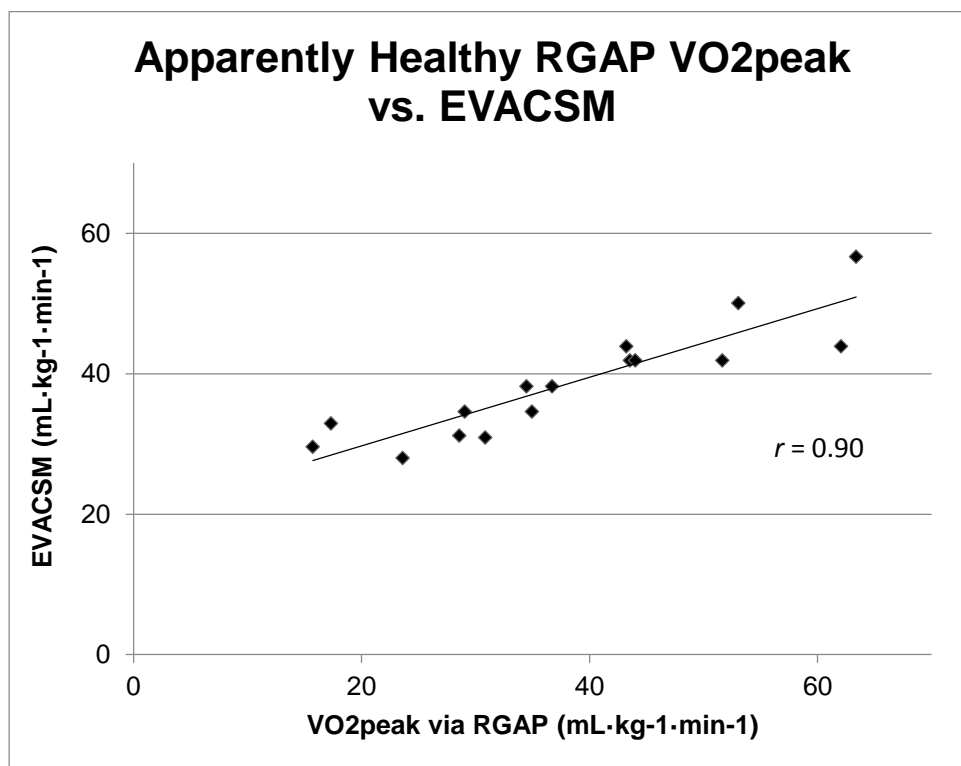


Figure 11. AH correlation between RGAP VO<sub>2</sub>peak and EVACSM

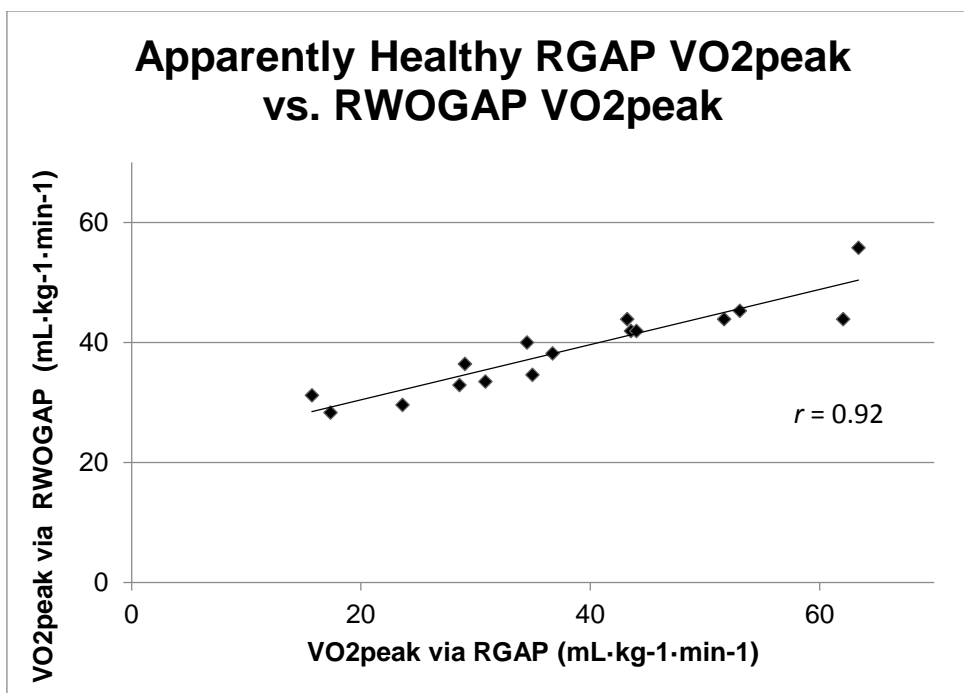


Figure 12. AH correlation between RGAP VO<sub>2</sub>peak and RWO GAP VO<sub>2</sub>peak

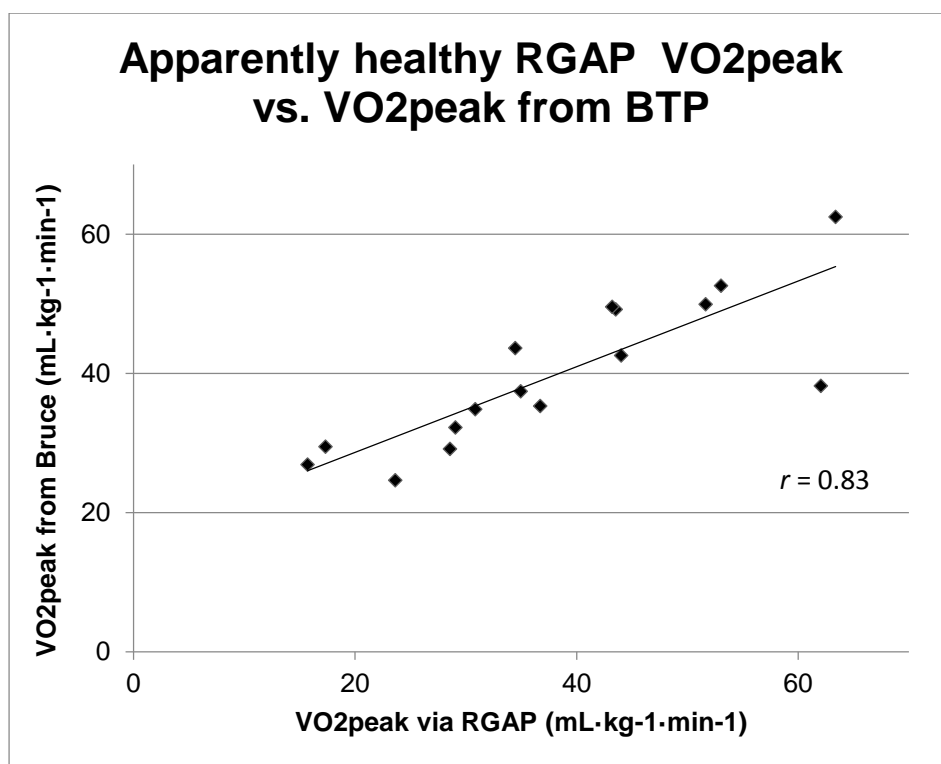


Figure 13. AH correlation between RGAP VO<sub>2</sub>peak and Bruce VO<sub>2</sub>peak Protocol

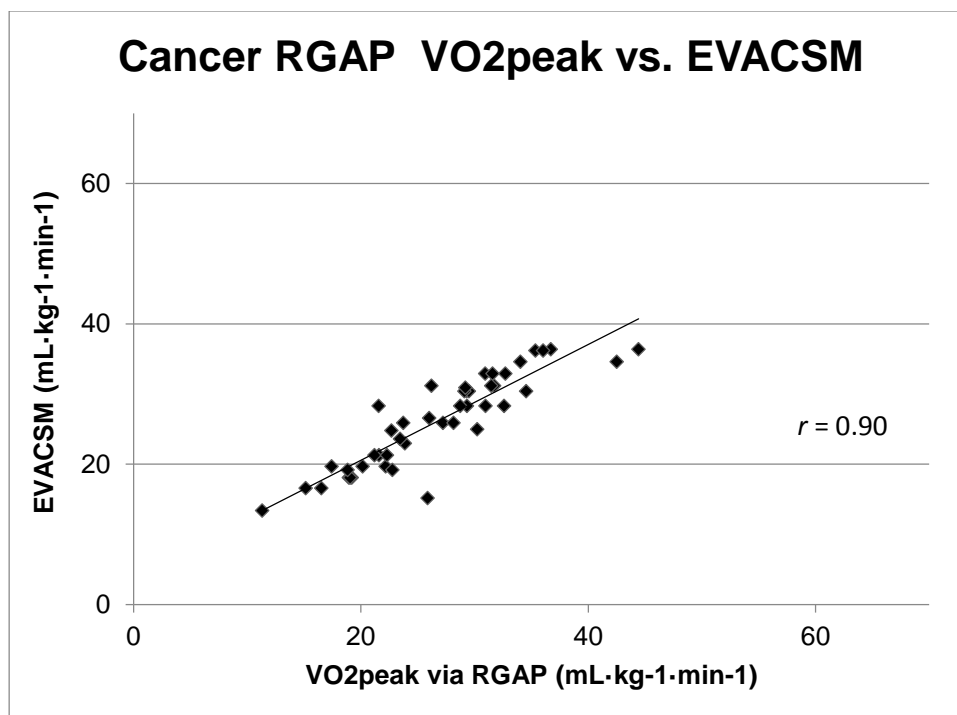


Figure 14. CS correlation between RGAP VO<sub>2</sub>peak and EVACSM

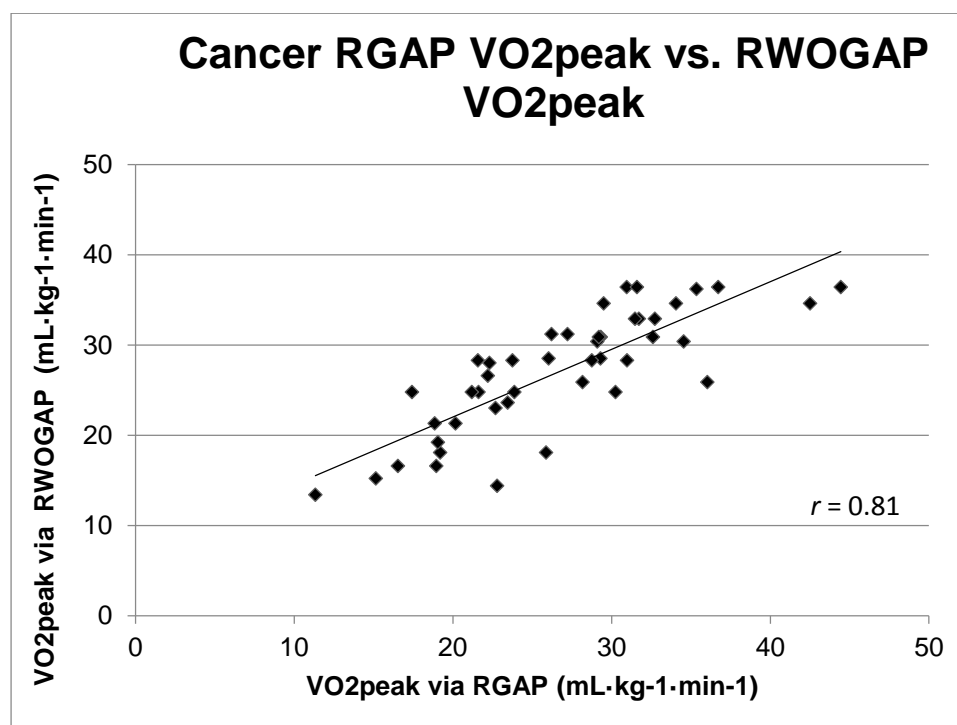


Figure 15. CS correlation between RGAP VO<sub>2</sub>peak and RWO GAP VO<sub>2</sub>peak



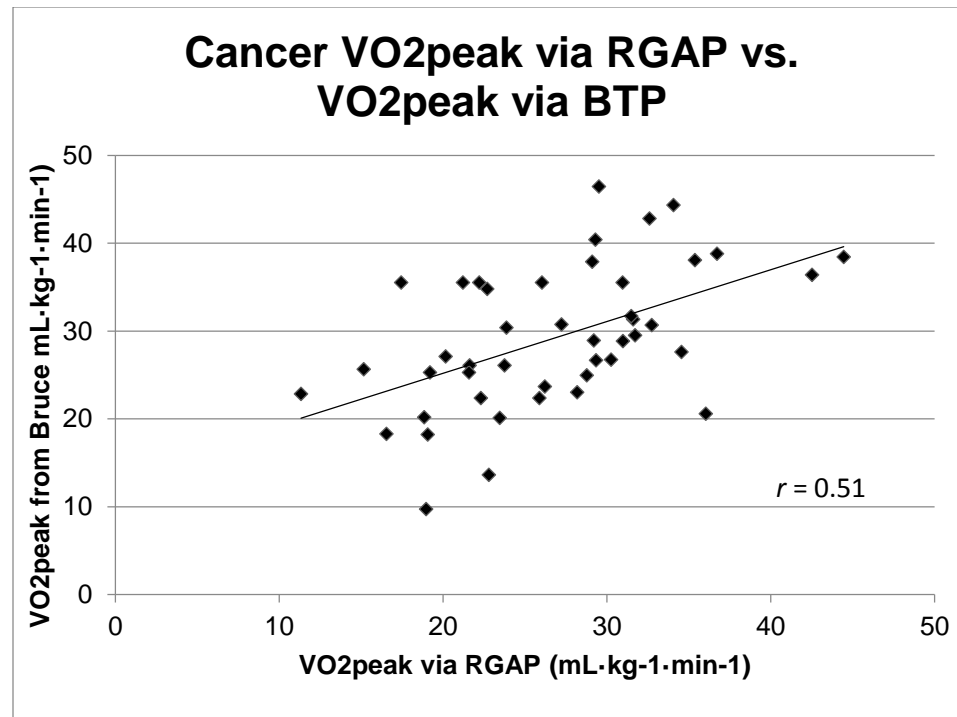


Figure 16. CS correlation between RGAP VO<sub>2</sub>peak and Bruce VO<sub>2</sub>peak Protocol

The statistical analysis repeated measures ANOVA test was confirmed to be an appropriate test to compare VO<sub>2</sub>peak values. The dependent variable (VO<sub>2</sub>peak) was a continuous value, the independent variables (RGAP, BTP, and RWO GAP) were all matched pairs, and there were no significant outliers in the related groups. Additionally, the VO<sub>2</sub>peak values were plotted on a histogram to illustrate the distribution of all VO<sub>2</sub>peak points. From this histogram, the dependent variable appeared to be approximately normally distributed. Due to all assumptions being met, along with the normal distribution of the data, the repeated measures ANOVA was the appropriate statistical test for this data.

## Discussion

The aim of this study was to assess the validity of the RMCRI multi-stage treadmill protocol for a cancer-specific population against standard metabolic gas analysis and the Bruce treadmill protocol. It was hypothesized that  $\text{VO}_{2\text{peak}}$  obtained from RMCRI gas analysis protocol would not significantly differ from  $\text{VO}_{2\text{peak}}$  calculated from the last completed stage of the GA test using ACSM's walking and running equations. This was confirmed for the CS and AH groups with a strong, positive correlation of  $r = 0.90$  observed for both. Similar correlations have also been reported between observed and predicted  $\text{VO}_{2\text{peak}}$  values for current valid  $\text{VO}_{2\text{peak}}$  protocols, such as the modified Balke treadmill test and the modified Naughton treadmill protocol (Ebbeling et al., 1991; Martin & Acker, 1988; Singh, Morgan, Hardman, Rowe, & Bardsley, 1994; Wolthuis et al., 1977). Ramp protocols such as the RMCRI protocol demonstrate a positive linear relationship between oxygen uptake and work rate (Myers et al., 1991), which would explain the non-significant differences between measured and estimated  $\text{VO}_{2\text{peak}}$  from the RGAP test. These findings confirm that using ACSM's walking and running equations are a valid method in determining  $\text{VO}_{2\text{peak}}$  for the RMCRI protocol. It also supports the notion that a metabolic cart is unnecessary to have during a cancer survivor's  $\text{VO}_{2\text{peak}}$  test if the ACSM equations produce accurate values that are not significantly different than those obtained through gas analysis.

All participants were able to safely and effectively complete each  $\text{VO}_{2\text{peak}}$  test, with no adverse effects experienced during or following a test. Given the general compromised state of the cancer population, many facilities may opt for a submaximal protocol (Furzer et al., 2012; Jones et al., 2008). However, the results of this study indicate that a cancer survivor can safely complete a  $\text{VO}_{2\text{peak}}$  test without any serious

complications, while still obtaining an accurate  $\text{VO}_{2\text{peak}}$  value. Wall et al. (2014) reported similar results with prostate cancer survivors completing a  $\text{VO}_{2\text{max}}$  treadmill test using a BTP. In that study 85% of participants reached  $\text{VO}_{2\text{max}}$  criteria without any adverse effects. They concluded that the risk of detrimental events during maximal testing is relatively low and was no higher than what is observed in age-matched control participants. Similarly, Scott et al. (2015) safely evaluated prostate cancer survivors using a modified Balke  $\text{VO}_{2\text{max}}$  test. In fact, 80% of the participants were able to complete two modified Balke  $\text{VO}_{2\text{max}}$  tests within a week without injury or adverse events. Many clinicians opt for the use of a submaximal  $\text{VO}_2$  tests because they appear safer than  $\text{VO}_{2\text{peak}}$  tests. However, multiple studies have concluded they are inaccurate for estimating  $\text{VO}_{2\text{max}}$  (Dabney & Butler, 2006; De Backer et al., 2007). Our findings agree with Scott et al. (2015) that a  $\text{VO}_{2\text{peak}}$  test appears appropriate and accurate for the cancer population.

In the cancer survivor group, peak Bruce heart rate was significantly lower than peak heart rate observed in both RMCRI protocols (RGAP and RWO GAP). This may be attributed to the steep inclines observed in the BTP. With steeper inclines, greater Type II muscle fibers are recruited, leading to utilization of anaerobic metabolism (Bottinelli & Reggiani, 2000; Boyas & Guevel, 2011; Westerblad, Bruton, & Katz, 2010). Byproducts of anaerobic metabolism such as cytokines or an accumulation of phosphate may have led to leg pain and muscular fatigue, possibly causing the CS group to prematurely terminate the test before reaching their true  $\text{VO}_{2\text{peak}}$ . Cancer survivors may be experiencing cancer cachexia and detrimental muscular toxicities due to treatment, thereby depleting ATP stores leaving patients severely fatigued even without physical

exertion (Berger, Gerber, & Mayer, 2012; Schneider & Hayward, 2013). The difficult intensities of the BTP may have exacerbated these decrements, resulting in termination due to muscular fatigue and not cardiovascular fatigue. Will et al. (1999) also observed difficulties achieving a target heart rate during the BTP in a general patient population. These researchers believed the poor performance was due to the physical inability to keep up with the large incremental workloads associated with stage progression. No significant differences were observed in peak HR, SBP, DBP, or RPE for the apparently healthy group between each protocol, as seen in other studies observing  $\text{VO}_{2\text{peak}}$  (Bader et al., 1999; Myers et al., 1991; Myers et al., 1992; Wall et al., 2014).

It was hypothesized that the  $\text{VO}_{2\text{peak}}$  achieved from BTP would be significantly lower than  $\text{VO}_{2\text{peak}}$  obtained from RMCRI gas analysis protocol for the cancer survivors. A strong positive correlation ( $r = 0.83$ ) and no significant differences were observed between these two protocols in the AH group. However, the CS group's peak  $\text{VO}_2$  values were in fact significantly higher in BTP when compared to the RGAP, and only a moderate positive correlation was observed between these protocols ( $r = 0.51$ ). The same significant observations were made when comparing the Bruce treadmill protocol  $\text{VO}_{2\text{peak}}$  values against the RWO GAP. Overestimation of  $\text{VO}_{2\text{peak}}$  in BTP has been observed before, and this is in agreement with Myers et al. (1991) who suggested that protocols with larger increments between stages may overestimate  $\text{VO}_{2\text{peak}}$ . Similarly, due to the greater magnitude of stage-based increases in exercise intensity seen with the BTP, a nonlinear relationship between oxygen uptake and work rate has been witnessed (Foster et al., 1984; Sullivan & McKirnan, 1984). Unlike the BTP, ramp protocols demonstrate a more linear relationship with work rate and oxygen uptake

(Myers et al., 1991), which may explain the significant differences in  $\text{VO}_{2\text{peak}}$  values between the RGAP and BTP.

Other studies have suggested that greater work rate increments as seen in the BTP may result in reduced exercised capacity (Foster et al., 1984; Redwood et al., 1971; Sullivan & McKirman, 1984), which disagrees with the findings in this study. However, equations for the Bruce protocol do not take into account an individual's limitations, such as the side effects of cancer or cancer treatments. The Bruce treadmill protocol may have yielded accurate values if the cancer survivors had not undergone cancer treatments. However, all CS received cancer-related treatments and the side effects may have significantly reduced the CS group's  $\text{VO}_{2\text{peak}}$ . This is commonly observed following cancer treatments due to physical inactivity (Blanchard, Courneya, & Stein, 2008; Coups & Ostroff, 2004; Kim et al., 2006; Murnane et al., 2012), which may have resulted in the overestimation from the BTP. The RMCRI protocol is intended to take these side effects into consideration using shorter and less intense stages, yielding a more accurate  $\text{VO}_{2\text{peak}}$  and a subsequently lower  $\text{VO}_{2\text{peak}}$  compared to the estimation from the BTP, which does not take those side effects into account. This may also explain why the BTP  $\text{VO}_{2\text{peak}}$  values did not significantly differ between any of the RMCRI protocols in the apparently healthy group. Results of this study suggest the RGAP has lower but more accurate values than BTP, which concurs with Myers et al. (1991) who stated that smaller work increments may yield a more accurate relationship between oxygen demand and supply at high levels of exercise, but may have slightly reduced values when compared with standard increments of ramp protocols.

The overestimation of the Bruce has important implications on the development of an individualized CS exercise prescription.  $\text{VO}_{2\text{peak}}$  is critical to have to accurately progress and improve cardiovascular health for a CS using exercise prescriptions (Heyward, 2013). Because the BTP over predicted  $\text{VO}_{2\text{peak}}$ , this could lead to a faulty exercise prescription due to the inaccurate  $\text{VO}_{2\text{peak}}$  value. With an over predicted value, a cancer survivor's exercise prescription will be inaccurate and may result in too difficult intensities for a CS to sustain. If a CS cannot tolerate the prescribed intensities from an exercise prescription, then no gains or progressions will be made. Without a reliable and accurate exercise prescription, a CS has no guidelines or instructions to follow that are needed to improve the deficiencies caused by the cancer and its treatments. The RMCRI protocol has been established to provide accurate  $\text{VO}_{2\text{peak}}$  values, and therefore is a critical protocol to use to provide useful values for an exercise prescription.

$\text{VO}_{2\text{peak}}$  did not differ between the RMCRI gas analysis protocol and the RMCRI without gas analysis protocol for both the cancer survivor and apparently healthy group. However, total treadmill time of the RWOGAP ( $12.66 \pm 3.01$ ) was significantly higher than treadmill time from the RGAP ( $12.12 \pm 2.82$ ) ( $p < 0.05$ ) for the CS group only. The AH group also had a greater treadmill time on the RMWOGA ( $16.87 \pm 3.96$ ) than the RGAP ( $16.62 \pm 4.31$ ), but this was non-significant. To our knowledge, this is the first study to address whether the metabolic cart, specifically the respiratory mask attached to the face of the participant, might hinder treadmill performance in cancer survivors. Anecdotally, multiple participants reported that the respiration mask was uncomfortable to wear and being unable to breathe normally through their noses made testing very difficult. Some participants stated the mask caused them to feel claustrophobic, causing

them to hyperventilate in a situation that already made it problematic to breathe normally. The difficulties experienced by our participants using the mask were not unfounded, as participants have reported shortness of breath, throat irritation, and dry mouth due to the different types of respiratory masks and mouth guards, all of which could cause a test to end prematurely (Baran et al., 2001; Bart & Wolfel, 1994; Gardiner & Ranalli, 2000; Hurst, 2004; Yarar et al., 2013). This might also explain the lower treadmill time on the RGAP.

Participants from both groups disliked how they could only look forward and not move their head in any other direction during the RGAP test. AH participants stated that not being able to look in any direction but forward made them concentrate more on their balance, as they were worried about tripping. Peripheral neuropathy and balance issues are a common side effect of cancer treatments (Stone et al., 2011; Wampler et al., 2007; Winters-Stone et al., 2011), and may be problematic for cancer survivors who are required to wear a piece of equipment that might aggravate this issue. If a participant is concentrating on balance instead of walking and physically exerting themselves, it may result in a lower and less accurate  $VO_{2peak}$  because the test was terminated due to reasons other than cardiovascular fatigue. This may explain the trending towards reduced, but non-significant, treadmill time for the AH group using the RGAP protocol. Even though  $VO_{2peak}$  did not significantly differ between these two protocols for either group, treadmill time was significantly affected in the CS group, which could result in lower overall  $VO_{2peak}$  values. This further supports the notion that GA is not the ideal scenario to test a cancer survivor's  $VO_{2peak}$ , even though it is the most accurate method. Our finding that  $VO_{2peak}$  from RGAP did not differ from estimated  $VO_{2peak}$  supports the notion that GA is

not required. Furthermore, the finding that the GA equipment may actually hinder performance substantiates this claim.

Total treadmill time significantly differed between the Bruce treadmill protocol and both RMCRI treadmill protocols (RGAP and RWOGAP) for both the CS and AH groups ( $p < 0.001$ ), however the RMCRI and BTP have drastically different stages. Because BTP consists of seven stages with each lasting three minutes and having greater magnitudes of changes in intensity with each stage, a participant is expected to fatigue earlier. The RMCRI protocol consists of 21 one-minute stages that gradually increase the magnitude of intensity, allowing a participant to go further into a test, and thus longer. Although a significant difference in treadmill time between the two protocols exists, this was expected as the RMCRI protocol is specifically designed to let a participant go further into the protocol. Additionally, 13% of the apparently healthy group was able to complete the entire RMCRI treadmill protocol, while none of the cancer survivor group were able to accomplish this feat. Furthermore, none of the total participants were able to complete the entire BTP. Because 13% of the AH group was able to finish the RMCRI protocol and not one could finish the BTP, this supports the notion that the BTP is an appropriate protocol for the AH population, but the RMCRI protocol may not be. The RMCRI protocol was designed to increase intensity in low magnitudes to account for cancer treatment side effects, so an individual that has had no cancer treatments may be able to better sustain the protocol and go further, increasing the chance of completing the protocol. The AH participants had no treatments related to cancer, allowing them to sustain the lower degree changes in intensity, which may explain why some were able to complete the entire protocol. Since none of the CS participants could finish the RMCRI



protocol, it seems fitting that this could be a treadmill protocol that is tailored specifically for participants suffering from cancer and cancer related treatments. 100% of the CS participants had received treatments related to cancer, which would explain why none of the CS participants could complete the protocol, yet an accurate  $VO_{2peak}$  was still achieved. The RMCRI protocol was designed for this very reason: easy to progress through but extremely difficult to complete for a cancer survivor suffering from cancer and cancer treatment side effects.

At the completion of all three treadmill tests, every participant was asked what protocol would be best for use with a cancer survivor population. It was unanimously agreed upon among all of the participants that the RMCRI protocol was best suited for a cancer survivor. When asked what the worst protocol for a cancer survivor to be tested on, 12 of the 16 participants in the apparently healthy group stated the Bruce treadmill protocol would be the worst, and four indicated that RGAP would be the worst. Many of the AH participants stated the inclines experienced during the BTP would be too much for a CS to handle. Subjects who thought the metabolic cart would be the worst protocol asserted the equipment attached to the face would make it unbearable for a patient.

### **Limitations and Future Directions**

There were several limitations to this study. First, the sample size for the apparently healthy control group was relatively small, and a greater number of control subjects would have been preferred to reduce statistical error. Second, all cancer survivors participants were already enrolled in the RMCRI program and had completed the RMCRI protocol during their initial assessment. Although the CS participants did not know the names of the protocol or specifically how each protocol would increase in

intensity, familiarity with the protocol could have played a role. This did not appear to have an effect on the results, but it should be considered for future data collection. Finally, participants may have performed better on the last completed protocol compared to the first protocol completed due to intra-rater reliability. The participants didn't know how any of the protocols progressed in intensity, but comfort to the environment and staff assisting with the tests may have grown over the three weeks, allowing a participant to go further on the last test.

It is possible that the RMCRI protocols were underestimating  $\text{VO}_{2\text{peak}}$  for CS, as average RER was 0.9. However, it is interesting to note that peak HR was significantly higher during both RMCRI protocols compared to the Bruce. It's plausible that CS resting RER was lower at rest compared to the AH group. Because gas analysis was not utilized during BTP, it is impossible to tell if resting and peak RER values were as low, if not lower, during BTP.

The ACSM walking and running equations that were used to calculate EVACSM were meant to calculate  $\text{VO}_{2\text{peak}}$  when an individual reached a steady state heart rate. For the RMCRI protocol, steady state may not have been achieved in the one minute stages. However, the findings that EVACSM did not significantly differ from RGAP suggests that ACSM's walking and running equations are appropriate to calculate  $\text{VO}_{2\text{peak}}$  for the RMCRI protocol, despite not reaching a steady state heart rate.

For future research, a greater sample size for a control group is suggested. This would decrease the risk of error in statistical analyses. Also, validating the RMCRI protocol to other less intense protocols would be useful, such as the modified Balke, the modified Naughton, the United States Air Force Treadmill protocol, or even the 6-Minute

Walk test. It would be beneficial to examine differences in  $\text{VO}_{2\text{peak}}$  values obtained from any of these protocols and the RMCRI protocol. An additional method of determining whether a participant reaches their true  $\text{VO}_{2\text{peak}}$  would be by taking blood lactate, which was not utilized in this study. Finally, it may also be useful to familiarize the participants with the three different treadmill protocols before starting the study. This way participants would know what to expect from each protocol, possibly allowing participants to go further, resulting in greater  $\text{VO}_{2\text{peak}}$ . Scott et al. (2015) found similar findings to this theory. After prostate cancer survivors'  $\text{VO}_{2\text{peak}}$  was tested twice within a week,  $\text{VO}_{2\text{peak}}$  was significantly higher on the second trial compared to the first trial, which may have been due to familiarity with the protocol.

## **Conclusion**

The present study examined the construct validity of the first cancer-specific treadmill  $\text{VO}_{2\text{peak}}$  assessment, the RMCRI multi-stage treadmill protocol.  $\text{VO}_{2\text{peak}}$  from the RMCRI gas analysis protocol did not significantly differ from EVACSM, suggesting gas analysis is not necessary during this protocol. Further supporting this claim, GA did appear to significantly decrease treadmill time, resulting in a lower  $\text{VO}_{2\text{peak}}$  value. The Bruce treadmill protocol utilizes large stage-related increases in exercise intensity which may be too difficult for cancer survivors to complete. This results in inaccurate values which supports our findings of significantly higher  $\text{VO}_{2\text{peak}}$  values from BTP compared to the RGAP test. The RMCRI protocol was specifically designed to decrease the magnitude of intensity experienced with each stage, allowing cancer survivors suffering from cancer and treatment-related side effects to progress further into the protocol, resulting in a more precise  $\text{VO}_{2\text{peak}}$  value. Obtaining an accurate  $\text{VO}_{2\text{peak}}$  value assists in

the development of an accurate exercise prescription, and is the first and foremost step in the design of a rehabilitation program. It is proposed that cancer rehabilitation clinics and facilities adopt the RMCRI treadmill protocol, which provides both patient comfort and accurate  $\text{VO}_{2\text{peak}}$  values.

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**APPENDIX A**

**PHYSICAL ACTIVITY READINESS  
QUESTIONNAIRE (PAR-Q)**

Physical Activity Readiness  
Questionnaire - PAR-Q  
(revised 2002)

# PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO	
<input type="checkbox"/>	<input type="checkbox"/>	1. Has your doctor ever said that you have a heart condition <u>and</u> that you should only do physical activity recommended by a doctor?
<input type="checkbox"/>	<input type="checkbox"/>	2. Do you feel pain in your chest when you do physical activity?
<input type="checkbox"/>	<input type="checkbox"/>	3. In the past month, have you had chest pain when you were not doing physical activity?
<input type="checkbox"/>	<input type="checkbox"/>	4. Do you lose your balance because of dizziness or do you ever lose consciousness?
<input type="checkbox"/>	<input type="checkbox"/>	5. Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?
<input type="checkbox"/>	<input type="checkbox"/>	6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?
<input type="checkbox"/>	<input type="checkbox"/>	7. Do you know of <u>any other reason</u> why you should not do physical activity?

If  
you  
answered

## YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

## NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active — begin slowly and build up gradually. This is the safest and easiest way to go.

- take part in a fitness appraisal — this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

## DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever — wait until you feel better; or
- if you are or may be pregnant — talk to your doctor before you start becoming more active.

**PLEASE NOTE:** If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

**Informed Use of the PAR-Q:** The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

**No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.**

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME \_\_\_\_\_

SIGNATURE \_\_\_\_\_

DATE \_\_\_\_\_

SIGNATURE OF PARENT \_\_\_\_\_

WITNESS \_\_\_\_\_

or GUARDIAN (for participants under the age of majority)

**Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.**



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continued on other side

**APPENDIX B****MEDICAL HISTORY FORM**



**Rocky Mountain Cancer Rehabilitation Institute**  
**Medical History**

**I. General Information**

Date \_\_\_\_\_  
 Name \_\_\_\_\_ Age \_\_\_\_\_  
 Current Primary Care Physician \_\_\_\_\_  
 Current Oncologist \_\_\_\_\_  
 Date of Last Complete Physical \_\_\_\_\_

Check ALL spaces below which apply to you. (If checked, please include explanation and date of occurrence.)

**II. Present Medical History**

**Explain and Date:**

_____ Rheumatic fever/heart murmur	
_____ High blood pressure	
_____ Chest discomfort	
_____ Heart abnormalities (racing, skipping beats)	
_____ Abnormal EKG	
_____ Heart problems	
_____ Coughing up blood	
_____ Stomach or intestinal problems	
_____ Anemia	
_____ Stroke	
_____ Sleeping problems	
_____ Migraine or recurrent headaches	
_____ Dizziness or fainting spells	
_____ Leg pain after walking short distances	
_____ Back/neck pain/injuries	
_____ Foot/ankle problems	
_____ Knee/hip problems	
_____ Lymphedema	
_____ High cholesterol	
_____ Diabetes	
_____ Thyroid problems	
_____ Lung disease	
_____ Respiratory problems/asthma	
_____ Chronic or recurrent cough	
_____ Disease of arteries	
_____ Varicose veins	
_____ Increased anxiety/depression	
_____ Recurrent fatigue	
_____ Arthritis	

**Medical History (page 2)****Present Medical History****Explain and Date:**

\_\_\_\_\_ Swollen/stiff/painful joints \_\_\_\_\_

\_\_\_\_\_ Epilepsy \_\_\_\_\_

\_\_\_\_\_ Vision/hearing problems \_\_\_\_\_

**Women Only**

\_\_\_\_\_ Currently pregnant \_\_\_\_\_

\_\_\_\_\_ Menstrual irregularities \_\_\_\_\_

\_\_\_\_\_ Number of children \_\_\_\_\_

Last mammogram: \_\_\_\_\_

Last pelvic/pap: \_\_\_\_\_

Breast self exam: Yes No

**Operations** (starting with the most recent)

1. _____	Date: _____
2. _____	Date: _____
3. _____	Date: _____
4. _____	Date: _____

**Hospitalizations** (reason) \_\_\_\_\_**III. Family Medical History**

_____ High blood pressure	Family member(s)? _____
_____ Heart attacks	Family member(s)? _____
_____ Heart surgery	Family member(s)? _____
_____ High cholesterol	Family member(s)? _____
_____ Stroke	Family member(s)? _____
_____ Diabetes	Family member(s)? _____
_____ Obesity	Family member(s)? _____
_____ Early death	Family member(s)? _____
_____ Cancer	Type? _____ Family member? _____
	Type? _____ Family member? _____
_____ Other familial illnesses (list)	

**IV. Medications**

List all current medications:

	<b>Medication:</b>	<b>Dosage:</b>	<b>Date Started:</b>
1.	_____	_____	_____
2.	_____	_____	_____
3.	_____	_____	_____
4.	_____	_____	_____
5.	_____	_____	_____
6.	_____	_____	_____

**Drug Allergies:**\_\_\_\_\_**Data Reviewed By** \_\_\_\_\_  
(signature)

## **APPENDIX C**

### **INFORMED CONSENT FOR PARTICIPATION IN RESEARCH**



Name \_\_\_\_\_ Date \_\_\_\_\_

**INFORMED CONSENT**  
**For Participation in Research at RMCRI**  
**Project Title:**  
**Exercise Interventions to Attenuate the**  
**Negative Side-effects of Cancer Treatments**

Rocky Mountain Cancer Rehabilitation Institute  
 Reid Hayward, Ph.D., Director  
 Phone Number: 970-351-1821  
[Reid.Hayward@unco.edu](mailto:Reid.Hayward@unco.edu)

Jessica Brown, M.S., Clinical Coordinator  
 Phone Number: 970-351-1724  
[Jessica.Brown@unco.edu](mailto:Jessica.Brown@unco.edu)

The Rocky Mountain Cancer Rehabilitation Institute (RMCRI) and the School of Sport and Exercise Science support the practice of protection of human subjects participating in research. The following information is provided for you to decide whether you wish to participate in either the standard RMCRI program or if recruited, specific research investigations. You should be aware that even if you agree to participate, you are free to withdraw at any time without affecting opportunities for participation in other programs offered by this department.

This program is involved with the assessment of your body composition, pulmonary function, cardiovascular endurance, muscular strength and endurance, range of motion and flexibility. Skinfold calipers will be used to measure body composition (body fat percentage). The pulmonary function test will be measured through maximum exhalation into a sterile mouthpiece. Measuring oxygen consumption on a motor-driven treadmill will assess your cardiorespiratory capacity. Assessment of muscular strength and endurance will occur through the use of weights, dumbbells, a handgrip dynamometer, and other established tests. Flexibility and range of motion will be measured by an instrument called a goniometer and by the modified sit-and-reach test. Baseline measurements such as: heart rate, blood pressure, height, weight, and circumference measurements will be taken for risk stratification and safety during your participation. Forms to be completed for the program include cancer history, medical history, lifestyle/activity questionnaire, and psychological tests such as depression scales,

quality of life, fatigue and cognitive functioning. Blood may be drawn with your permission at various time points during your participation. Once all of the tests are completed, the results will be analyzed and an exercise prescription will be written. You may then have the option of participating in a three month exercise intervention based on your testing results. The expected benefits associated with your participation in this program include information regarding your level of physical fitness and recommended fitness and lifestyle changes necessary to improve your quality of life and health.

If you are recruited, and agree to participate in a specific research investigation, additional exercise, psychological, and/or cognitive tests may be administered. Your optional three month exercise intervention may also differ, but the expected benefits should still include improved quality of life and health.

All participants at RMCRI will be under the direction of the RMCRI Director and Clinical Coordinator but other persons will be associated or assist with the data collection. Your participation is solicited, although strictly voluntary. The obtained data may be used in reports or publications but your identity will not be associated with such reports. We at RMCRI, take mental distress that may accompany health issues seriously and will attempt to support you with counseling referrals and information on local cancer support groups if this is an issue. Our staff is required to report evidence of clear and imminent danger.

This research should not result in physical injury, however, some soreness may occur and some of the fitness tests can be uncomfortable. Additionally, with the blood draws you may feel temporary discomfort. The duration of the discomfort is short. Please give your consent with full knowledge of the nature and purpose of the procedures, the benefits that you may expect, and the discomforts and/or risks which may be encountered. We appreciate your assistance.

“Participation is voluntary. You may decide not to participate in this study and if you begin participation, you may still decide to stop and withdraw at any time. Your decision will be respected and will not result in loss of benefits to which you are otherwise entitled. Having read the above and having had an opportunity to ask any questions, please sign below if you would like to participate in this research. A copy of this form will be given to you to retain for future reference if requested. If you have any concerns about your selection or treatment as a research participant, please contact the Office of Sponsored Programs, Kepner Hall, University of Northern Colorado Greeley, CO 80639; 970-351-2161”.

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**Signature of Subject Agreeing to Participate**

*By signing this consent you certify you are at least 18 years of age.*

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**Signature of Researcher**

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**Date**

---

**Signature of Physician**

---

**Date**

**APPENDIX D****INSTITUTIONAL REVIEW BOARD APPROVAL**

UNIVERSITY of  
NORTHERN COLORADO



*Institutional Review Board*

DATE: April 8, 2014

TO: Reid Hayward, PhD  
FROM: University of Northern Colorado (UNCO) IRB

PROJECT TITLE: [573297-2] Exercise Interventions to Attenuate the Negative Side-Effects of Cancer Treatments

SUBMISSION TYPE: Amendment/Modification

ACTION: APPROVED

APPROVAL DATE: April 4, 2014

EXPIRATION DATE: April 4, 2015

REVIEW TYPE: Expedited Review

Thank you for your submission of Amendment/Modification materials for this project. The University of Northern Colorado (UNCO) IRB has APPROVED your submission. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on applicable federal regulations.

Please remember that informed consent is a process beginning with a description of the project and insurance of participant understanding. Informed consent must continue throughout the project via a dialogue between the researcher and research participant. Federal regulations require that each participant receives a copy of the consent document.

Please note that any revision to previously approved materials must be approved by this committee prior to initiation. Please use the appropriate revision forms for this procedure.

All UNANTICIPATED PROBLEMS involving risks to subjects or others and SERIOUS and UNEXPECTED adverse events must be reported promptly to this office.

All NON-COMPLIANCE issues or COMPLAINTS regarding this project must be reported promptly to this office.

Based on the risks, this project requires continuing review by this committee on an annual basis. Please use the appropriate forms for this procedure. Your documentation for continuing review must be received with sufficient time for review and continued approval before the expiration date of April 4, 2015.

Please note that all research records must be retained for a minimum of three years after the completion of the project.

If you have any questions, please contact Sherry May at 970-351-1910 or [Sherry.May@unco.edu](mailto:Sherry.May@unco.edu). Please include your project title and reference number in all correspondence with this committee.

This letter has been electronically signed in accordance with all applicable regulations, and a copy is retained within University of Northern Colorado (UNCO) IRB's records.



## **APPENDIX E**

### **FEELING SCALE IN EXERCISE SCALE**

**Feeling Scale (FS)**  
(Hardy & Rejeski, 1989)

While recovering from cancer and cancer treatments, it is common to experience good days, normal days, and not-so-good days. Researchers have developed a scale to measure such experiences. On the scale below, circle the number that indicates how you feel physically today.

+5      Very Good

+4

+3      Good

+2

+1      Fairly good

0        Neutral

-1      Fairly bad

-2

-3      Bad

-4

-5      Very bad

## **APPENDIX F**


### **ROCKY MOUNTAIN CANCER REHABILITATION INSTITUTE TREADMILL PROTOCOL**

Client Name: \_\_\_\_\_

Date: \_\_\_\_\_

Prior to testing take resting HR, BP, and Weight

Date of Birth: \_\_\_\_\_ Age: \_\_\_\_\_ RHR: \_\_\_\_\_ RBP: \_\_\_\_\_

Body Weight (lbs): \_\_\_\_\_  Kg (lbs/2.2): \_\_\_\_\_ Phase: \_\_\_\_\_

Max HR: \_\_\_\_\_

**RMCRI Cancer Treadmill Protocol Worksheet**

Stage	Speed	Grade	Time	BP	HR	RPE	SpO <sub>2</sub>
0	1.0mph	0%	1 min				
1	1.5mph	0%	*				
2	2.0mph	0%	*				
3	2.5mph	0%	*				
4	2.5mph	2%	*				
5	3.0mph	2%	*				
6	3.3mph	3%	*				
7	3.4mph	4%	*				
8	3.5mph	5%	*				
9	3.6mph	6%	*				
10	3.7mph	7%	*				
11	3.8mph	8%	*				
12	3.9mph	9%	*				
13	4.0mph	10%	*				
14	4.1mph	11%	*				
15	4.2mph	12%	*				
16	4.3mph	13%	*				
17	4.4mph	14%	*				
18	4.5mph	15%	*				
19	4.6mph	16%	*				
20	4.7mph	17%	*				
Cool-Down	**	0%	*				

\*Identify time for each the final stage and for the cool-down

\*\*Identify speed for cool-down

Note: If client changes from a walk to a run during this test, identify the time when the gate changed.

Was the client holding the handrails?      Yes      No

Was the client running during the last stage completed?      Yes      No

VO<sub>2</sub> Peak (L/Min) : \_\_\_\_\_

VO<sub>2</sub> Peak (mL/kg/min) :

\_\_\_\_\_

FINAL TIME to peak/volitional fatigue: \_\_\_\_\_ as a decimal

\_\_\_\_\_

## **APPENDIX G**

### **BRUCE TREADMILL PROTOCOL**

Client Name: \_\_\_\_\_

Date: \_\_\_\_\_

- Prior to testing take resting HR, BP, and Weight

RHR: \_\_\_\_\_ RBP: \_\_\_\_\_ Phase: \_\_\_\_\_ Max HR: \_\_\_\_\_

Body Weight (lbs): \_\_\_\_\_ → Kg (lbs/2.2): \_\_\_\_\_ DOB: \_\_\_\_\_ Age: \_\_\_\_\_

- Prior to testing, allow subject a 2–3 minute warm-up at a pace below protocol pace; explain procedures (purpose, BP, HR, RPE)

Test Protocol:                      Submax                      Max                      Peak

Stage	Time	Speed	% Grade	HR	BP	RPE	SpO <sub>2</sub>	Comments
Warm-Up	2-3 Min.	1.7	0%					
1	3 min.	1.7	10%					
2	3 min.	2.5	12%					
3	3 min.	3.4	14%					
4	3 min.	4.2	16%					
5	3 min.	5.0	18%					
6	3 min.	5.5	20%					
7	3 min.	6.0	22%					

\*Identify time for each the final stage and for the cool-down.      \*\*Identify speed for cool-down.

Note: If client changes from a walk to a run during this test, identify the time when the gate changed.

Was the client holding the handrails?      Yes      No

Was the client running during the last stage completed?

Yes

No

**Recovery Data (Cool-Down):**

Minute	HR	BP	RPE
1			
2			
3			
4			
5			

Comments:

**VO<sub>2</sub> Peak (L/Min) :** \_\_\_\_\_**VO<sub>2</sub> Peak (mL/kg/min) :** \_\_\_\_\_**FINAL TIME to peak/volitional fatigue:** \_\_\_\_\_ **as a decimal** \_\_\_\_\_



## **APPENDIX H**

### **ABBREVIATIONS**

## *Abbreviations*

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ACSM	– American College of Sports Medicine
AH	– apparently healthy
BP	– blood pressure
BTP	– Bruce treadmill protocol
CES	– Cancer Exercise Specialist
CHF	– congestive heart failure
CRF	– cancer related fatigue
CS	– cancer survivor
DBP	– diastolic blood pressure
DOX	– doxorubicin
EVACSM	- estimated max volume of oxygen consumption using last completed stage of the Rocky Mountain Cancer Rehabilitation Institute gas analysis protocol
FEV1	- forced expiratory capacity
FRS	- Framingham risk score
FVC	– force vital capacity
GA	– gas analysis
HR	– heart rate
METS	– metabolic equivalent
O <sub>2</sub>	– oxygen
PAR-Q	– physical activity readiness questionnaire
QOL	– quality of life
RBP	– resting blood pressure
RDBP	– resting diastolic blood pressure
RER	– respiratory exchange ratio
RGAP	– Rocky Mountain Cancer Rehabilitation Institute gas analysis protocol
RHR	– resting heart rate
RMCRI	– Rocky Mountain Cancer Rehabilitation Institute
RPE	– rating of perceived exertion
RSBP	– resting systolic blood pressure
SAS	- Statistical Analysis System
SBP	– systolic blood pressure
SPO <sub>2</sub>	- blood oxygen saturation
SPSS	- Statistical Package for the Social Sciences
UNC	– University of Northern Colorado
VO <sub>2</sub>	– volume of oxygen consumption
VO <sub>2peak</sub>	– peak volume of oxygen consumption
VO <sub>2max</sub>	– maximum volume of oxygen consumption

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